Exhibit 55

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCT MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***This Document Relates to All Cases***	**Civil Action No. 3:16-md-2738-MAS-RLS** **MDL No. 2738**

AMENDED EXPERT REPORT OF

MICHELE L. COTE, PH.D., M.P.H.

Dated: May 28, 2024

Michele L Cote

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Scientific Review of the Epidemiologic Evidence Regarding the Association Between Use of Perineal Talcum Powder and Epithelial Ovarian Cancer

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I. My Mandate

I was retained to perform a methodological review and to render my professional opinion regarding the question: Can the use of perineal talcum powder cause epithelial ovarian cancer? When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products. As a cancer epidemiologist, I have expertise in observational study methodology, data collection and analysis, and interpretation of epidemiologic data as it pertains to carcinogenesis. In order to synthesize the research in this area, as I do in my daily work, I considered the totality of evidence, including findings from the fields of pathology, oncology, toxicology, cancer biology, environmental health, and exposure science in order to render an opinion regarding causality.

I am compensated at a rate of $400 per hour for the literature review and completion of this written report. I have not testified as an expert in any cases during the previous four years.

II. My Credentials, Expertise and Experience

I received my Bachelor of Science in Biology from the University of Michigan, Ann Arbor, followed by my Master of Public Health with a concentration in Epidemiology from the University of Alabama, Birmingham. From there, I worked for the Oklahoma State Department of Health as an epidemiologist in infectious disease and maternal and child health for approximately 3 years. I returned to Michigan in 1999 and worked as a project coordinator at Wayne State University (WSU) on a case-control study of lung cancer genetics while simultaneously earning my doctorate in Epidemiologic Sciences at the University of Michigan, Ann Arbor in 2004.

I accepted a tenure-track faculty position at WSU in 2005 and remained there until 2022, climbing the ranks from Assistant Professor to Professor (with tenure). I also served as the Associate Center Director for Cancer Research Training and Education from 2016 until my departure from WSU. Finally, in 2019 I assumed leadership of the Environment and Cancer Research Interest Group for the NIEHS-supported Center for Urban Responses to Environmental Stressors (CURES) where I facilitated collaborative projects between toxicologists, molecular biologists, community outreach specialists and epidemiologists with a focus on cancer research. Prior to that time, I had been involved with CURES since 2016 as the co-Leader of Career Development.

In September of 2022 I moved to Indiana University as the Director of the Komen Tissue Bank, housed at the Simon Comprehensive Cancer Center (SCCC) at Indiana University in Indianapolis, Indiana. As part of my Directorship, I am the Carrie Ann Glasscock West Endowed Chair of Breast Carcinogenesis. In addition, I am a tenured Professor of Epidemiology at the Fairbanks School of Public Health in the Department of Epidemiology at Indiana University in Indianapolis, Indiana. I am a full member of the SCCC Cancer Prevention and Control program.

I am a nationally and internationally recognized cancer epidemiologist, evidenced by over 3 dozen invited lectures at cancer centers and other health-related institutions and conferences across the world, and another dozen regionally/locally. My accomplishments in the field were recognized by my peers in 2020, when I was awarded the John Snow Award from the Epidemiology Section of the American Association of Public Health. This award, named after the “father of modern epidemiology”, honors an outstanding epidemiologist for excellence in epidemiologic practice or research.

As a scientist my original research has been supported by various foundations (Susan G. Komen for the Cure, LUNGevity, etc.) and the National Cancer Institute (NCI) over the past two decades. I have published extensively in the realm of gynecologic cancers, from etiology to survivorship, including in ovarian cancer. Specific to my mandate, approximately 1/3 of the 155 peer-reviewed manuscripts I have published to date have examined ovarian cancer as an outcome. As a member of the research team for the African American Cancer Epidemiology Study (AACES), a case-control study of African American women with and without ovarian cancer, we published a manuscript examining genital talc use and ovarian cancer in 2016, as well as various other studies examining other risk factors.[1] This research continues as a survival cohort, the only one of its kind to focus on African American women.

My expertise in methodology and synthesis of data allows me to successfully work across different cancer types. For example, in lung cancer, I was the primary author of a systematic review which included a large meta and pooled analysis examining germline polymorphisms and risk. I was also the primary author of a methodologically similar publication examining family history and lung cancer with the International Lung Cancer Consortium, and a lung cancer review I co-authored is listed as the "Top Read" articles in *Cancer Epidemiology, Biomarkers and Prevention* (as of October 2023).[2–4] I am currently a long-standing member of the Publications and Proposals committee for the Women's Health Initiative (a prospective cohort study) and I am the Principal Investigator on two cohort studies (the Komen Tissue Bank and Benign Breast Disease: The Detroit Cohort). I have developed study protocols and questionnaires, identified study participants, collected, managed and analyzed novel data from both case-control and cohort studies. The methods I use have been passed down to hundreds of students via didactic teaching and mentoring graduate students. The high quality of my teaching and mentoring was recognized by Wayne State University in 2018 when I was selected to receive the Outstanding Graduate Mentor Award in Health Sciences.

As with my research, my teaching has predominantly focused on best practices for applying epidemiologic methods to human health challenges. I have led or co-led introductory courses in epidemiology as well as an applied epidemiology course at the graduate level for over a decade. In addition, I have given a wide variety of guest lectures in environmental health, chronic disease, and taught research methods to genetic counseling students. I have served as Chair or co-Chair of three doctoral committees that have focused on breast or ovarian cancers and have mentored over two dozen graduate-level trainees.

My vision as to the best way to develop the next generation of scientists and my adeptness at working across disciplines resulted in two training grant awards as a Principal Investigator (PI). The first, the Komen Graduate Training in Health Disparities Research program (co-PI, Manohar Ratnam, PhD, a basic scientist), funded three doctoral students annually and was one of only a handful of programs funded across the United States. The second award, the Initiative for Maximizing Student Development, was a T32 funded by the National Institutes of Health and supported 10 doctoral students annually across the biomedical sciences. The other PIs on this award were professors in pharmacology and chemistry, showing the range of my interdisciplinary collaborations.

In addition to research and teaching, I provide service to my field through providing expert peer review of manuscripts, grants, and scientific programs. I review on average 10 manuscripts annually for national and international journals, such as the *American Journal of Epidemiology*, *Carcinogenesis, Cancer Epidemiology, Biomarkers and Prevention, Gynecologic Oncology, the Journal of Clinical Oncology*, and *The Lancet*. I have been an associate editor for *Cancer Research* and the *Journal of the National Cancer Institute*. My expertise has been requested by numerous national and international scientific review panels including the NCI, the National Heart, Lung and Blood Institute, the National

Institute on Minority Health and Health Disparities, Komen for the Cure, the French National Cancer Institute, the National Institute for Health Research--United Kingdom, and the Netherlands Organization for Scientific Research. In addition to these manuscript and grant reviews, I have also reviewed programs, including serving on review panels for NCI-designated comprehensive cancer centers and NCI intramural programs. These program reviews are usually onsite and include assessment of both written materials and oral presentations. They require the ability to assimilate components across various clinical and research programs and assess the strengths and weaknesses of the research of the institute or program both individually and as a whole.

While my expertise is in the area of epidemiology, primarily in female cancers and health disparities, I regularly read studies from various medical fields including pathology, oncology, gynecology, physiology, molecular biology, and exposure science. I have experience and expertise based on two decades of developing my own scientific hypotheses, and then writing grant proposals and scientific manuscripts that address the questions. Synthesizing information from across disciplines is one of my core strengths as a scientist and teacher, and I bring the same approach to addressing the current mandate. Additional details regarding my academic record can be found in my curriculum vitae, attached as Appendix A.

III. Executive Summary

This review focused on the assessment of epidemiologic literature, including hypothesis-testing meta-analyses, pooled analyses, cohort studies, and case control studies. My review included over 3 dozen peer-reviewed published research studies. I also reviewed systematic reviews and reports from various agencies, with a focus on the reports from the International Association for Research on Cancer (IARC) and Health Canada, as both had detailed information about the methods and procedure describing the compilation of the documents. The published manuscripts and the government reports usually discussed the potential underlying mechanisms driving the association between perineal talc and ovarian cancer, so I reviewed basic science work in this area as well. Additional details are available in the full report.

The epidemiologic evidence is consistent with respect to the association between perineal talc use and epithelial ovarian cancer. The meta- and pooled analyses were consistent in reporting a positive association between ever versus never perineal talc use and ovarian cancer, with estimates ranging from 12 to 47% increased risk, and statistically significant. The 4 cohort studies reported lower, but still positive, associations between perineal talc use and ovarian cancer, with estimates ranging from 0.73 to 1.12. The lowest estimate was from the Sister Study, which showed in later work that their restriction to the timing of the exposure underestimated the actual exposure. Finally, of the 23 case-control studies, (which were summarized in the meta and pooled analyses as well as analyzed independently), 19 (82.6%), indicate a positive association between perineal talc use and ovarian cancer risk. The majority (12 of 19) of the positive associations were statistically significant at a 95% confidence level. Further, the case-control studies were more likely to collect detailed exposure information, and 64.2% of the 14 case-control studies that collected this information reported a positive association.

Based on their systematic review published in 2010, IARC classified talc-based body powder without asbestiform fibres as a 2B (possibly) carcinogen. An earlier report from 1987 reported that talc not containing asbestiform fibres should be considered a Group 3 Carcinogen (“not classifiable as to their carcinogenicity to humans”). Thus, from the report in 1987 until 2010, talc not containing asbestiform fibres moved from a Group 3 to a Group 2b agent. Talc with asbestos has remained classified as group

1 ("carcinogenic to humans"), as was talc containing asbestiform fibers. In 2021, the Health Canada screening report concluded that talc constitutes or may constitute a danger in Canada to human life or health. It concluded that the current data (as of 9/2021) on talc and ovarian cancer are indicative of a causal effect. The Health Canada assessment was on talc alone without considering whether or not talc contained asbestos.

Published studies in humans have shown that talc can migrate from the perineum to the ovaries and surrounding tissue. The putative mechanism is the inflammatory response caused by the talcum powder, resulting in chronic inflammation and oxidative stress, which may initiate the carcinogenic process. In addition to talc (platy and fibers), other chemicals such as asbestos, heavy metals and fragrances have been found in samples of talcum powder from Johnson & Johnson products.

In order to best synthesize all of the data from various lines of evidence, I utilized a process formally described by medical epidemiologist and statistician, Sir Austin Bradford Hill, in 1965 which included nine viewpoints by which to evaluate human epidemiologic evidence to determine if causation can be deduced: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. In the case of perineal talc exposure and ovarian cancer, I found evidence supporting nearly all of these viewpoints with strength, consistency and plausibility to be strongly weighted in my decision. Specificity, temporality, biologic gradient, and coherence were apparent, but more moderately weighted factors. The overall estimate of effects in most studies and the summary estimates from the meta-analyses are of a magnitude (~1.25) that is comparable to other common exposures that are causally related to cancer.

In my opinion, as an epidemiologist and cancer researcher, stated to a reasonable degree of scientific certainty, use of talcum powder products, including Johnson & Johnson Baby Powder and Shower to Shower, in the genital/perineal area can cause ovarian cancer. I base this opinion on the elevated measures of effect (relative risk, odds ratios), most of which are statistically significant when combined into meta or pooled analyses, the pathological evidence, the consistency of results across multiple populations, geographic areas, and in different race/ethnic groups, the evidence of a positive dose-response effect, and the plausible biological mechanisms.

IV. The Science of Epidemiology

Epidemiology is an observational science. The Greek origin of the word breaks down into "epi"—around or upon—and "demos", people. A standard definition is that epidemiology describes the determinants and distribution of disease in populations, with the goal of identifying areas to intervene. These interventions ultimately result in reducing the burden of the disease in the population. Note, however, that actual interventions are outside of the scope of epidemiology. Observational studies are used when it would be unethical or otherwise too difficult to examine an association between an exposure and an outcome.

Epidemiology relies on various study designs and methodology that are specific to the field. Case studies, where a new condition is described, or sometimes a new presentation of an established disease, are one basic type of study. Case series would describe several similar cases. These types of studies are rudimentary but may be the first indication of a disease circulating in a population and may provide the earliest hypotheses regarding factors that are associated with the disease (e.g., the human immunodeficiency virus in California).[5] Cross-sectional studies, another type of epidemiologic study, assess disease and exposure at the same time in a population that is not selected for either an

exposure or an outcome, and are regarded as useful for hypothesis-generating, but not hypothesis-testing. Ecologic studies are similar to cross-sectional studies in that they gather exposure and outcome data at the same time, but the unit of analysis is a population (a city, state or country, for example). Data are usually identified from secondary sources, such as deaths due to respiratory conditions (from vital records) and air pollution levels in different states (based on monitoring by the EPA, for example). Again, ecologic study designs are hypothesis-generating versus hypothesis-testing.

The two study designs in epidemiology that are appropriate for hypothesis-testing are case-control and cohort studies. Case-control studies are utilized when the disease is relatively rare in the population and consist of identifying and recruiting individuals with the disease (cases) and those without (controls) into a research study. The measure of effect for case-control studies is the odds ratio. Conversely, cohort studies recruit individuals into a study based on exposure, which may be something such as birth cohort (e.g., Women's Health Initiative) or identification as belonging to a certain profession (e.g., Nurses' Health Study), and follows them forward in time to see what conditions develop. Hence, cohort studies are useful to look at several outcomes, whereas case-control studies can only examine one outcome. The measure of effect for cohort studies is generally the relative risk or hazard ratio. These terms are described in greater detail below.

I would not describe one study design as better than another, as all epidemiologic studies have strengths and limitations. Even randomized controlled trials (which are interventional and thus do not fall under epidemiologic studies), often considered the gold standard in human research, may have biases and other flaws that limit their utility. Thus, it is important to consider all evidence as a whole with consideration given to the strengths and weaknesses of each study. There are ways to aggregate data from single studies into a larger study, with the goal of improving the power to detect associations between exposures and outcomes. Meta-analyses, which combine estimates of the measures of association from multiple single studies into one overall estimate, and pooled analyses, which utilize individual-level data from multiple studies to estimate a single measure of association, are two types of studies at aggregate data.

The following terminology may be useful when considering the rest of this report:

•Bias is a systemic error that can occur during the design, recruitment, data collection or analysis phases of a study that results in an incorrect estimation of the true effect between the exposure and the outcome. Different study designs are prone to different biases, as described below.

•Chance: Whether a random error is responsible for the association identified. Chance is commonly assessed through use of a confidence interval or p-value.

•Confidence interval: Based in probability, a confidence interval is calculated to correspond with a measure of effect (or effect measure). If the underlying statistical model is correct and there is no bias, a confidence interval will, over unlimited repetitions of the study, contain the true measure of association with a frequency no less than its confidence level (usually 95% in epidemiologic studies).

•Confounding: A type of bias that can occur when a third variable interferes with a true relationship between an exposure and an outcome. A confounding variable is one that is related to the risk of disease and also to the exposure. It is not by itself a cause of the disease. Confounding is reduced in multivariate analyses by including potential confounding variables in the model.

•Effect modification: Variation in the measure of effect for the factor under study across levels of another factor (e.g., a hypothetical example: the odds ratio for the association between smoking and

lung cancer is different for men compared to women—here, gender is the variable that modifies the association).

•Hazard ratio: Also used in cohort studies, hazard ratios differ from relative risk estimates in that relative risks are cumulative over an entire study, using a defined endpoint, while hazard ratios represent instantaneous risk over the study time period, or some subset thereof. They are interpreted in a similar manner.

• Incidence rate: a measure that describes new cases of disease in a population over a period of time. Can be calculated from cohort, but not case-control studies. Estimates can be standardized to compare rates across different populations or adjusted for the age structure of the population.

•Latency period: The interval between exposure to the disease-causing agent until the disease is clinically recognized (diagnosed).

•Misclassification: A form of information bias, this occurs when an exposure or outcome (disease) is not accurately reported or captured. This can alter the measure of effect "away from the null" (meaning the effect measure is bigger than what is true) or "towards the null" (meaning the effect measure is smaller than what is true). Differential misclassification occurs when the misclassification differs by outcome status whereas non-differential misclassification does not differ by outcome status. Both case-control and cohort studies can have issues with misclassification. A specific type of differential misclassification, known as recall bias, is described below.

•Odds ratio: The usual measure of effect calculated in case-control studies. It is calculated by the ratio of the odds of exposure among cases to the odds of exposure among controls. In situations where the disease is relatively rare in the total population, as is the case for most cancers, the odds ratio approximates the relative risk.

•Power: A statistical concept that measures the ability of a study to demonstrate an association between a risk factor and disease if one exists. The power of a study is determined by several factors, including the frequency of the condition under study, the magnitude of the effect, the study design, and sample size. Mathematically, power is defined as the probability that the null hypothesis will be rejected if it is false, and is equal to $1 - \beta$, where β is the probability of type ii error (failing to reject a false null hypothesis).

•p-value: The probability that if you repeated the study, you would find a result at least as extreme, assuming the null hypothesis is true. The p-value quantifies the likelihood of getting the data that you got if the null hypothesis did happen to be true, not that your hypothesis is indeed true. The size of a p-value depends on the sample size, the effect size, and the consistency of the data.

•Risk factor: An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic (germline genetics, for example) that can be measured and may be associated with disease. Risk factors may be modifiable (e.g., diet, physical activity, use of products) or nonmodifiable (e.g., age, ancestral background).

•Recall bias: A type of systematic error (and differential misclassification) due to differences in accuracy or completeness of recall to memory of past events or experiences that varies by case or control status. Case-control studies may be more prone to this type of bias. It should be noted that this is not a case of participants "not remembering", which would be more likely to lead to nondifferential misclassification. The key difference is that recall varies by the outcome of interest.

•Relative risk: The usual measure of association calculated in cohort studies, it is calculated by dividing the incidence rate among the exposed by the incidence rate among the unexposed

•Sample size: A component to consider when assessing the power of a study, this is the number of people in the study population. Those with the disease are the most critical factor for both study designs.

•Selection bias: There are various forms of selection biases, but the general concept is that the association between the exposure and the disease is different for those who are selected to participate in the study. This can be the result of low response rates (both case-control and cohort studies) or loss to follow up (cohort studies).

•Type I and Type II errors: Type I errors occur with a null hypothesis is incorrectly rejected (i.e., declaring that a difference exists when it does not). A Type II error is failing to reject a false null hypothesis (i.e., declaring that no difference exists when one actually does).

V. The Epidemiology of Ovarian Cancer

Ovarian cancer is the deadliest gynecologic cancer, with an expected 19,710 new cases diagnosed and 13,270 deaths from the disease in 2023 in the United States alone according to estimates from the American Cancer Society.[6] The most common type of ovarian cancer, high grade serous epithelial, is thought to originate in the fallopian tubes, thus these cancers are often described along with epithelial ovarian cancers.[7,8] Peritoneal cancers, which are very rare, are also generally grouped with ovarian cancers due to similarities in the cell type of origin, behavior, and prognosis.[9] The average age at diagnosis is 63 years, and the overall 5 year survival rate for epithelial ovarian cancer is 50%, although this varies by stage, as well as race, with African American women having the poorest survival after an ovarian cancer diagnosis.[10] Table 1 describes survival by stage at diagnosis, using classifications from the Surveillance, Epidemiology and End Results (SEER) program, a population-based cancer registry.

Table 1: Relative survival rates by time since ovarian cancer diagnosis, by SEER stage, for cancers diagnosed from 2000-2019

Stage* (% diagnosed)	**5 year (% surviving)**	**10 year (% surviving)**
Local (17.5)	92.3	88.7
Regional (19.9)	73.1	65.3
Distant (54.4)	30.2	17.6
Unstaged (8.1)	36.2	29.2

*Local stage is when the cancer is confined to the primary site, Regional stage is when the cancer has spread to the lymph nodes, Distant stage is when the cancer has metastasized. Stage at diagnosis was for cancer diagnosed from 2011-2020

Unlike cervix cancers, with established screening and now a vaccination that reduces risk of Human Papilloma Virus (HPV), or endometrial cancers, which generally present as post-menopausal bleeding with the tumor still localized to the uterus at diagnosis, ovarian cancer does not have any population-based screening modalities or distinct symptoms at presentation. While many women with ovarian cancer present with gastrointestinal concerns or weight loss, often these symptoms aren't present until the disease has progressed.[11] Thus, these cancers tend to be diagnosed in later stages, with greater morbidity and mortality (as shown in Table 1).

Histologic subtypes of ovarian cancer

Histologic subtypes are differentiated based on the cell of origin, molecular alterations, and clinical behavior. A four-marker immunohistochemical panel can distinguish the five principal histologic types shown in Table 2 with high accuracy.[12]

Table 2: Common histologic subtypes of ovarian cancer

Type	Serous		Endometrioid	Clear Cell	Mucinous
	High Grade	Low grade			
Proportion	70%	<5%	10%	10%	3%

A grading system was established nearly two decades ago that also categorizes serous ovarian tumors as high or low grade.[13] High grade serous tumors appear to arise primarily from fallopian tube epithelium or ovarian epithelium, so much so that the 2020 WHO Classification of Female Genital Tumours now uses the combined terminology of tubo-ovarian high-grade serous carcinoma.[14] Low grade serous cancers also originate in the same manner, but have mild to moderate nuclear atypia and fewer mitoses compared to their high grade counterparts with marked atypia and greater mitoses counts.[15] Endometrioid and clear cell tumors arise from the ovarian epithelium or endometriosis.[12] Mucinous ovarian cancers are relatively rare and the cell of origin has been unclear, with concerns that these are not ovarian but metastases from other primary sites, such as the gastrointestinal tract.[16] Thus, misclassification of these tumors may have occurred in earlier studies without the technologies that have been developed over the last decade (e.g., somatic molecular testing). A recent study by Cheasley et al. has shown that mucinous ovarian carcinoma arise from mucinous borderline ovarian tumors and can progress to high grade mucinous ovarian cancer, indicating that with further molecular analysis mucinous ovarian cancers can be distinguished from metastatic disease of non-ovarian origin, such as gastrointestinal tumors.[17] In addition to these histologic types, mixed ovarian tumors also occur, as do undifferentiated carcinomas. Mixed cell types are as described: mixtures, to various degrees, of the other histologic types of ovarian cancer. Undifferentiated ovarian cancers lack distinguishing characteristics for further classification and tend to be aggressive, with a poor prognosis.[18,19] Finally, borderline ovarian cancers are epithelial tumors that represent 10-20% of all ovarian epithelial tumors. They have some malignant features, such as cell proliferation and nuclear atypia, but do not show infiltrative (invasive) growth patterns. Prognosis is significantly better for these tumors.[20]

The histologic subtypes described above represent the vast majority (90%) of ovarian cancers and are epithelial in origin. Thus, the review presented here focuses on epithelial ovarian cancers.

Risk factors

Risk factors are often categorized as modifiable or non-modifiable. Risk factors for ovarian cancer that are non-modifiable include: increasing age, nulliparity, greater height, a history of endometriosis, and having a family history of breast and/or ovarian cancer.[21–23] There are several known inherited syndromes that increase ovarian cancer risk as well, including *BRCA1* and *BRCA2* mutations, Hereditary nonpolyposis colon cancer syndrome (also known as Lynch Syndrome), and other rarer familial syndromes.[24,25]

Modifiable risk factors that increase the risk of ovarian cancer include being overweight or obese, use of post-menopausal hormone therapies, and genital use of talcum powder.[22] Use of oral contraceptives,

intrauterine device (IUD) use, aspirin, and breastfeeding are modifiable factors that appear to reduce the risk of ovarian cancer.[21,26,27]

A woman with an intact reproductive system (uterus, ovaries, fallopian tubes) also known as a patent reproductive tract, is at greater risk for ovarian cancer than a women with a hysterectomy and bilateral salpingo-oophorectomy (removal of uterus, both ovaries and fallopian tubes), or a bilateral or unilateral salpingo-oophorectomy.[28,29] These procedures can be indicated for other reasons, but have been offered as risk-reduction strategies for women with known inherited mutations (i.e. *BRCA1* or *BRCA2* mutation carriers). Women who have undergone a tubal ligation, a method of contraception that is generally not reversable, also appear to have lower risk of ovarian cancer compared to women who have not undergone a tubal ligation.[30,31] The distinction as to whether a woman has a patent reproductive tract is relevant to the discussion of biological mechanisms, as described in the next section.

VI. The Exposure: Talc

Talc is a naturally occurring mineral mined from the earth, composed of magnesium, silicon, oxygen and hydrogen.[32] Talc is usually platy (growing in sheets or plates) but may also occur as asbestiform fibres or fibrous talc (asbestiform refers to a pattern of mineral growth—not to be confused with talc that contains asbestos).[33]

i. Other Substances in Johnson & Johnson Talc Products

Platy talc has been used widely in various cosmetic and personal care products, including talcum powder products sold by Johnson & Johnson such as Johnson's Baby Powder and Shower to Shower. In addition to platy talc, talcum powder often contains asbestos and almost always contains talc fibers. Drs. Longo and Rigler examined historical samples of Johnson & Johnson's products from 1960-2003 (not all years were represented) and found that 68% of the samples contained asbestos and 98% of the samples contained fibrous talc.[34] Internal testing by Johnson & Johnson with testing done sporadically from 1957-1992 showed various samples contained asbestos and/or talc fibers.[35] As recently as October 18, 2019, the FDA updated a Safety Alert and issued a Constituent Update warning consumers not to use certain cosmetic products that tested positive for asbestos, after a sample of Johnson's Baby Powder tested positive for asbestos and talc fibers (Johnson's Baby Powder Lot #22318RB).[36] The Final Rule from the Environmental Protection Agency (EPA) of the "Asbestos; Reporting and Recordkeeping Requirements Under the Toxic Substances Control Act", published July 25, 2023, recognizes the co-occurrence of asbestos and talc as such: "EPA maintains that talc and vermiculite are some examples of the bulk commodities that may contain asbestos as an impurity."[37]

In addition to asbestos and fibrous talc, there is evidence that talc contains heavy metals that are known to be carcinogenic. As described in the deposition of Julie Pier, talcum products have been shown to contain chromium, cobalt and nickel.[38] A recent study by Almugren et al. tested 4 talcum powder products currently available in Malaysia, including Johnson's Baby Powder, and noted all contained nickel, arsenic and lead.[39] Other constituents of talcum powder are fragrance chemicals that have been identified as carcinogenic or inflammatory agents. Dr. Crowley, a chemist with a doctoral degree in molecular pharmaceuticals, noted the following after an examination of Johnson's Baby Powder and Shower to Shower: Johnson's Baby Powder contained a mixture of 141 fragrance chemicals, some of which were a mixture of chemicals.[40] Shower to Shower contained a fragrance mixture comprising 53 fragrances, some of which are mixtures themselves. Between the two products,

there were at least 175 fragrance chemicals. Forty-two of the fragrance chemicals (22 in Johnson's Baby Powder and 20 in Shower to Shower) were identified with a regulatory concern. Some were classified by the Environmental Protection Agency (EPA) or the International Agency for Research on Cancer (IARC) as potentially carcinogenic. Dr. Crowley classified almost all of these agents as irritants, sensitizers, and/or allergens. He concluded that these chemicals contained inflammatory properties and were potentially carcinogenic.[40]

ii. Johnson & Johnson Discontinuation of Talc-based Johnson's Baby Powder

As described above, Johnson & Johnson recalled 33,000 bottles of Johnson's Baby Powder in October 2019 after the United States Food and Drug Administration (US FDA) found asbestos in a bottle it tested.[36] On May 19, 2020, Johnson & Johnson released the following statement, (found on the Johnson & Johnson "Facts About Talc" website, www.factsabouttalc.com last accessed November 11, 2023)[41]:

> "The Company will wind down the commercialization of talc-based Johnson's Baby Powder in the U.S. and Canada in the coming months. Existing inventory will continue to be sold through retailers until it runs out. Cornstarch-based Johnson's Baby Powder will remain available in North America. Both types of Johnson's Baby Powder – talc-based and cornstarch-based – will continue to be sold in other markets around the world where there is significantly higher consumer demand for the product."

On August 12, 2022, Johnson & Johnson announced that it would discontinue sales of talc-based powder worldwide in 2023, moving to a cornstarch-based product. [42] Per Johnson & Johnson's "Facts About Talc" website[41]:

> "Thousands of tests repeatedly confirm that our consumer talc products do not contain asbestos. Our talc comes from ore sources confirmed to meet our stringent specifications. Not only is our talc routinely tested to ensure it does not contain asbestos, our talc has also been tested and confirmed to be asbestos-free by a range of independent laboratories and universities."

This statement directly contradicts the US FDA report (and others, see Longo and Rigler[34]) finding asbestos in their testing of Johnson & Johnson Baby Powder that led to the cessation of sales of the product.

iii. "Facts About Talc" and Cancer-related Lawsuits

The "Facts About Talc" website goes on to say, "The weight of the science does not support any claim that our talc products cause cancer" but only includes a handful of studies, and none of them are directly referenced. Further, the American Cancer Society link that is referenced (http://www.cancer.org/cancer/cancercauses/othercarcinogens/athome/talcum-powder-and-cancer) is no longer online (as of November 12, 2023).

There is a link provided by the "Facts About Talc" website under the "Review the Evidence" tab that links to a Dropbox containing over 3,200 documents from 2018, last modified September 12, 2022.[41] In my opinion, it is unreasonable to think that a member of the general public would be able to comprehend and decipher all of these documents in a way that would allow them to draw a meaningful conclusion regarding the safety of talc. Finally, under the "News" tab, there are many statements in

response to the various ongoing litigations for both mesothelioma and ovarian cancer, which give the illusion of full transparency.

iv. Cornstarch as a Safer Alternative

Cornstarch, a cooking staple in many kitchens, is the replacement for talc suggested by Johnson & Johnson. In 1948, a publication by Eberl et al. stated that cornstarch would be an "entirely satisfactory replacement" for talcum powder on surgical gloves, due to it being bioabsorbable and non-irriatating.[43] Motivated by interest in the talcum powder and ovarian cancer associations being reported in the literature, a review article was published in 2000 comparing the chemical natures of talcum powder and cornstarch in the peritoneal cavity.[44] They noted that cornstarch could be removed by physiologic processes from the cavity, it did not contain asbestos, and that no epidemiologic studies had identified an association between cornstarch use and ovarian cancer.

VII. Biologic Mechanisms Linking Perineal Talc and Ovarian Cancer

Insight as to how talc products and their components can migrate from the perineum through the genital tract to the ovaries and fallopian tubes was first gleaned from research attempting to understand human fertility and contraception. In 1957, Hartman described " cooperation by the musculature of the female genital tract" as a way that sperm moves distally.[47] In 1961, Egli and Newton describe the movement of carbon particles placed in the vagina to the fallopian tubes (in approximately one half hour) in two of three women examined.[48] A similar experiment in 1972, using India ink (a suspension of carbon) placed in the vagina, uterus or cervical canal of 178 women found evidence the ink traveled to the fallopian tubes at least half of the time when placed in the uterus.[49] In 1979, radioactive tracers were noted to travel from the vagina to the uterus or the tubes and ovaries in 16 of 21 (76%) of the women; in the 5 negative cases, it was noted that the patients had "severe tubal occlusion due to previous infections."[50]

Specific to talc, animal studies followed (which would allow for different conditions such as longer duration after the agent was placed) and noted that for rabbits (n=3) and monkeys (n=8) there was no evidence of translocation of talc when administered.[51–53] As reviewed by Lynch et al.[54], this was different for rats, with all rats receiving intrauterine talc installations having talc particles found in the ovaries of all rats upon sacrifice, regardless of length of administration. For those receiving intravaginal talc exposure, a longer period of time was needed (talc was found in the ovaries after 4 days, but not 1 or 2 days).[55] Thus, animal studies do not provide consistent evidence of translocation of talc—it may be species-dependent.

Human studies provide evidence in that talc particles have been identified in ovarian tissue in women with and without ovarian cancer.[54] In 1971, Henderson used electronic microscopy and identified talc in 75% of ovarian tumors (10/13), 42% (5/12) of ovarian tissue from women who were having oophorectomies due to a breast cancer diagnosis, and 57% (12/21) of cervical tumors.[56] In 1996, Heller et al. examined ovaries from 24 women undergoing incidental oophorectomy, 50% reported regular perineal talc use. Evidence of talc in the ovaries was found in all women, which the authors suggest was due to widespread exposure to talc during diapering.[57] In 2019, McDonald et al. found talc in all five ovarian cancer patients with talc exposure at multiple sites (two or more of the following: pelvic region lymph nodes, cervix, uterine corpus, fallopian tubes, and ovaries), and also noted macrophages were a key part of the tissue response to the migrated talc.[58] Finally, in 2020, Johnson et

al. used updated microscopy methods (bright field, differential interference contrast (DIC), polarized light microscopy (PLM), and scanning electron microscopy (SEM) with energy dispersive X-ray analysis (SEM/EDX)) to examine both talc-containing baby powder (including Johnson & Johnson) and resected tissue from women with ovarian cancer.[59] They used 11 randomly selected patients to achieve 200 talc particles within pelvic tissues resected at surgery for detailed study of particle size and shape. They noted that most particles between the talc products they tested and what was found in the pelvic tissue were small and isodiametric and similar to what was reported by McDonald et al.[58] In their discussion, they noted that they had recently presented a larger analysis of particles and fibers in pelvic tissue at a recorded, public US Food and Drug Administration meeting in February 2020.[60] At that time, they reported that 196 ovarian cancer cases (with a history of talc use) had been studied by polarized light microscopy and birefringent particles were found in the pelvic tissues of 180 (92%) of those patients. Of those cases, 91 had been studied by SEM/EDX and 82 (90%) were found to have talc particles. These studies suggest that perineal use of talc can and does make its way into tissues in the reproductive tract, including the ovaries and fallopian tubes.

Sjosten et al. provided real-time evidence of retrograde migration of starch powders in humans, including talc from surgical gloves which could be found in tissues after hysterectomy. They recruited 58 women undergoing hysterectomy for benign conditions and allocated them to one of four arms, based on time from gynecological exam (1 day/4 days preoperatively) and powder/no powder gloves. Cell smears were taken from the peritoneal fluid and during the operation further smears were taken from the fallopian tubes, uterine cavity and cervical canal. Significant differences were found for large starch particles at all locations between the study and control groups examined 1 day pre-operatively. Considering small starch particles, there were differences in cervix ($p< 0.001$), uterus ($p< 0.01$) and the fallopian tubes ($p< 0.01$), providing evidence in humans of retrograde migration of starch powder in humans.[61] Retrograde menstruation has been noted in healthy women at least 20 years prior to the study by Sjosten et al., based on laparoscopy of 323 women. Halme et al. noted that retrograde menstruation through the fallopian tubes into the peritoneal cavity is very common in women with patent tubes (90%), although less so in women without patent tubes (15%).[62]
There are multiple lines of evidence suggesting that talc exposure induces several markers of inflammation. Macrophages are part of the innate immune response. A study published by Keskin et al. examined long-term talc exposure on the genital system of female rats. The preliminary results showed that talc given intravaginally daily for 3 months, had unfavorable effects on the female genital system, similar to that of a foreign body reaction or infection.[63] In vitro, Mandarino et al. noted that the presence of variable macrophage, giant cell, or lymphocytic infiltrates in talc-exposed human tissues depending on the patient and anatomic site.[64] Additionally, exposure of macrophages to talc (particularly in the presence of estradiol) was shown to increase production of reactive oxygen species (ROS) and changes in expression of macrophage genes important in cancer.[64] Buz'zard et al. also noted in ovarian cancer cell lines that talc increased production of ROS, which play rolls in the modulation of cell survival, differentiation, cell signaling, and inflammation-related factor production.[65] Fletcher et al. used normal and ovarian cancer cell lines to examine the effects of talc exposure. They reported that talc-exposed cells had a dose-dependent increase in key pro-oxidants (chemicals that increase oxidative stress) and a decrease in antioxidant enzymes (control or reduce cellular damage) compared to controls. The tumor marker CA-125 also increased, as did cell proliferation and a reduction in apoptosis (programmed cell death that removes "unhealthy" cells).[66] In summary, as reviewed by Savant et al., talc attracts macrophages, which try to phagocytose it to remove it from the body. The macrophages then send chemical signals, triggering the response of other immune mediators and initiating a wound healing process. As talc is not degradable by the body, it inhibits the wound healing process, resulting in chronic inflammation.[67]

VIII. Overview of My Methodology

A key component to successfully obtaining external grant funding is the assessment of the rigor of the prior research that serves as support for the proposed project. The main areas where rigor are especially critical are the background and the methodology sections. In the background, a rigorous proposal should assess all of the current research in the area, identify weaknesses of prior research and gaps in current knowledge. A summary of these data is critical to convincing reviewers that you understand the prior work in this area and that your application will produce novel, high impact discoveries that will ultimately improve human health. As a grant reviewer, rigor is an area that drives the impact of the application. I assess whether the application has identified relevant research in the area, the conclusions that have been drawn from that research, and whether alternative explanations have been considered. The second area where rigor is crucial is in the approach, or the methodology that will be used to address the research question. When examining the proposed approach, I consider the study design, methodology, and planned analysis. The methods proposed in the approach should contain enough detail that they could be replicated elsewhere, and their use should be justified. I used the concept of rigor as the foundation for this review of the literature addressing the question, "Can the use of perineal talcum powder cause epithelial ovarian cancer?"

I performed an initial literature review following PRISMA guidelines for systematic reviews, utilizing PubMed and Web of Science using search terms including combinations of "talc", "ovarian cancer", "body powder" and "fallopian tube cancer" and generated lists of peer-reviewed publications.[68] I cross-referenced my searches to make sure I had identified all relevant work to the best of my ability. In each article, I examined the reference sections in these publications to add to my review. My focus was on epidemiologic studies, although I reviewed others that described the possible mechanisms of carcinogenesis proposed when examining the association between talc and ovarian cancer. During my reviews, I also identified several government reports from across the globe regarding genital talc use and risk of ovarian cancer.

IX. Epidemiologic Evidence: Perineal Talc and the Risk of Ovarian Cancer

The first studies suggesting an association between use of talc and ovarian cancer were published in the 1970's (Henderson WJ, 1971, 1979) and dozens of case-control studies and a handful of cohort studies have since examined the hypothesis that there is an association between use of perineal talc and ovarian cancer. Below I summarize the studies and my interpretation of their main findings, starting with the most recent publications.

i. Systematic Reviews

The Government of Canada released a FINAL Screening Assessment of Talc (Environment and Climate Change—Health Canada) in April 2021, a finalized version of the draft released in 2018.[69] Of note, this report specifically assumed cosmetic-grade talc "to be asbestos free" (per page 4) and covered both the potential harm to the environment as well as harm to human health. Of interest here is risk to human health, and various routes of exposure were considered, including oral, dermal, inhalation, and perineal. Through a detailed assessment of both animal and human studies, including epidemiologic studies that will be described in greater detail below, inhalation exposure was considered to be a human health risk for non-cancer lung effects such as impaired lung function, inflammation, and fibrosis. With respect to perineal exposure, the consistency of the positive association seen across multiple populations, coupled with biological plausibility, built support for the conclusion that there was a causal effect between perineal talc exposure and ovarian cancer. Consideration of these multiple lines of evidence prompted additional restrictions warning of inhalation risks to adults and cancer links in females who use talc-based products for personal care. The Health Canada report concluded that the association between use of perineal talc and ovarian cancer was causal.

The International Agency for Research on Cancer, known as IARC, has published 3 monographs that examined talc. The most recent, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100 C, Arsenic, Metals, Fibres, and Dust was published in 2012. This report focused on Group 1 carcinogens, those that are viewed to be carcinogenic to humans. It notes that asbestos can take several forms, including those determined to be carcinogenic: serpentine (chrysotile) and amphibole (actinolite, amosite, anthophyllite, crocidolite, and tremolite) minerals.[33] In this monograph, IARC noted that talc deposits may contain actinolite, anthophyllite, and tremolite forms of asbestos. Talc may also form fibers that are asbestiform in habit, meaning they have greater strength, flexibility and durability. This type of talc, referred to as fibrous talc, has also been classified by IARC as a Class 1 human carcinogen. Therefore, both talc containing asbestiform fibers (i.e., talc fibers) and talc containing asbestos should be considered carcinogenic to humans. This report, updated from the earlier 1987 Monograph, supported asbestos and talc containing asbestiform fibers as a causal agent for ovarian cancers.[33,70]

In 2010, another report was published, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 93, Carbon Black, Titanium Dioxide, and Talc. This report focused on talc that did not contain asbestiform fibers. The report considered scientific evidence available as of 2006, including epidemiologic data from 1 cohort and 19 case-control studies. These studies, while not all reporting effect estimates at the level of statistical significance, were homogenous across studies with increases of risk ranging from 30-60% higher among users of talc in the perineal region versus those who did not. The overall conclusion of this report was that perineal use of talc-based power is possibly carcinogenic to humans—Group 2b. Essentially, this means that evidence supporting risk to humans is limited, and evidence from animal models is lacking; however, it is a higher level of concern than Group 3 ("not classifiable as to their carcinogenicity to humans") or Group 4 (""probably not carcinogenic to humans"). These reports were an update from the 1987 IARC Monograph that considered talc containing asbestiform fibres a Group 1 Carcinogen and talc not containing asbestiform a Group 3 Carcinogen ("not classifiable as to their carcinogenicity to humans"). Thus, talc not containing asbestiform fibres moved from a Group 3 to a Group 2b agent (and talc containing asbestiform fibres remained at this highest level, Group 1).

Overall, the reports from IARC in 2010 and the Government of Canada are the collective work of dozens of national and international experts across a variety of disciplines. While only considering data as of 2006, IARC concluded that with respect to perineal use and ovarian cancer, talc without asbestiform fibers is possibly carcinogenic to humans. The report from Health Canada (which included data as of 2021) goes a step further to assess the association as causal.

ii. Meta-analyses

Twelve meta-analyses have been published examining the perineal use of talc and risk of ovarian cancer. While these studies do not rely on novel data collection (unlike the case-control and cohort studies reviewed later), they do compile, analyze and interpret data from other studies.

The vast majority report a statistically significant increased risk of ovarian cancer in ever users of perineal talc. Most of the studies published in the last decade include an assessment of study quality, and some attempt to provide estimates based on duration or frequency of application or stratify by tumor histologic type. While containing a larger number of cases and controls compared to single studies, there are still limitations. Specifically, there are challenges in trying to harmonize questionnaire data where the exposure information is worded differently or asks about specific time periods. The benefit is the larger sample size, which allows for stratification (by tumor subtype, for example). It should also be noted that the vast majority of these studies, including the larger cohort studies, are primarily of non-Hispanic white women. African American women, who generally report greater use of perineal talc, comprise less than 10% of all study participants, with the exception of the case-control

study presented by Schildkraut et al. which recruited only women who self-identified as African American or Black.[1] Brief summaries of the 12 meta-analyses are presented below, starting with the most recent contributions to the literature.

In 2022, Phung et al. utilized data from 9 studies in the Ovarian Cancer Association Consortium (OCAC) which was focused on risk factors for ovarian cancer in women with and without endometriosis. Combined, there were 8,500 women with ovarian cancer and13,592 controls (although the Dutch study did not collect information on talc use and was thus not included in this specific analysis). Genital talcum powder use showed increased ovarian cancer risk, and risk appeared greater for those with endometriosis vs. those without (genital talcum powder: OR = 1.38; 95% CI, 1.04-1.84 vs. OR = 1.12; 95% CI, 1.01-1.25, respectively). The authors suggest that this finding provides evidence that inflammation is a mechanism driving ovarian carcinogenesis, as both endometriotic and adipose tissues produce proinflammatory cytokines that have been shown to increase the risk of ovarian cancer.

In 2022, Woolen et al. performed a systematic review of the literature with the goal of identifying studies that captured data on frequency of use of talc in the perineal region, versus typical meta-analyses that categorized people as never or ever. Of all identified studies, 1 were included in the analysis (case-control, 1 cohort). Frequency of use was captured various ways, with the minimum appearing to be “at least 4 times a week” and the higher end of the frequent exposure being 10,000 applications. The estimated a summary odds ratio of 1.47 (95% CI 1.31, 1.65) for multiple times per week users. Sensitivity analyses (removing a study that was not considered “high quality” and removing the single cohort study) did not appreciably alter the estimate. The only cohort data came via the Nurses’ Health Study I from O’Brien, as this study had the required frequency of use data. There were 1,224 confirmed ovarian cases in this analysis versus 1,055 reported in the O’Brien pooled analysis from 2020. The adjusted hazard ratio for daily users was 1.27 (05% CI; 1.09, 1.49) compared to non-users; this was higher when restricted to women with patent fallopian tubes (HR=1.40, 95% CI: 1.17, 1.68).[71] What differentiates this systematic review and meta-analysis is the inclusion of studies that captured frequency of use, versus the dichotomous never/ever use of talc. As such, the measures of effect were larger, particularly for estimates restricted to women with patent fallopian tubes.

In 2021, Davis et al. published findings from the Ovarian Cancer in Women of African Ancestry consortium. This pooled analysis from 5 studies, including 620 African American women with ovarian cancer, 1,146 African American controls, and 2,800 white women with ovarian cancer and 6,735 controls. Each study had to have at least 40 African American women with ovarian cancer to participate. Four population-based case-control studies and a nested case-control study from the Women’s Health Initiative (WHI) were included. Individual-level data were harmonized across studies. Eligibility was restricted by interview year to prior to 2014, due to the potential to be influenced by the class action lawsuits filed in 2014. The goal of the Davis et al. manuscript was to examine the association between genital powder use and epithelial ovarian cancer risk between African American and white women, overall, by histologic type, and frequency/duration. With the exception of the African American women in WHI, all single site analyses showed increased risk associated with ovarian cancer and use of genital powder, and the overall pooled risk was OR=1.32 (95% CI: 1.17-1.48) after adjustment for age, education, duration of oral contraceptive use, family history of breast cancer, family history of ovarian cancer, tubal ligation, full-term pregnancies, interview year, body mass index, menopausal status and smoking. Adjusted pooled risk estimates were similar for African American women (OR=1.22, 95% CI: 0.97-1.53) and white women (OR=1.36, 95% CI: 1.19-1.57). When stratified by subtype and frequency, elevated risk remained, particularly for those with high-grade serous subtypes (greater than once a week use, OR_{AA}=1.34, 95% CI: 1.02-1.76; OR_{white}=1.29, 95% CI: 1.08-1.54), although the trends were not statistically significant. There were no trends seen for duration (less than or equal to 20 years, greater than 20 years). The authors acknowledge the potential for recall bias in the case-control studies but argued that restricting data to information collected prior to 2014 would limit this bias, and misclassification would likely be nondifferential (and thus bias the results

towards the null). The study concluded that while genital powder use was more prevalent in African American women, the associated risk estimates did not differ by race.

In 2020, O'Brien et al. performed a pooled analysis of 4 large U.S. cohort studies: Nurses' Health Study (enrollment 1976; follow-up 1982-2016; n = 81,869—talc data collected 1982), Nurses' Health Study II (enrollment 1989; follow-up 2013-2017; n = 61,261—talc data collected in 2013), Sister Study (enrollment 2003-2009; follow-up 2003-2017; n = 40,647—talc data limited to one year before baseline, or at ages 10-13), and Women's Health Initiative Observational Study (enrollment 1993-1998; follow-up 1993-2017; n = 73,267). There were 2,168 women who developed ovarian cancer, with a median follow up time of 11.2 years. The overall hazard ratio estimate for any use compared to no use was 1.08 (95% CI, 0.99 to 1.17). Additional analyses to reveal associations with frequency and duration found similar estimates for frequent vs never use (HR=1.09, 95% CI: 0.97 to 1.23) but no association between long-term vs never use (HR=1.01, 95% CI: 0.82 to 1.25). A final analysis, restricted to women with patent reproductive tract reported a HR of 1.13 (95% CI: 1.01 to 1.26), which was higher when the exposure was defined as "frequent" use of at least once per week (HR=1.19 (95% CI: 1.03, 1.37). The restriction of the analysis to women who have an intact reproductive tract is an important consideration, because if the mechanism driving ovarian carcinogenesis requires talcum powder to travel up the vagina and through the cervix, women with patent reproductive tracts would be more susceptible to the effects of powder use in the genital area on ovarian cancer. The study authors concluded that, "there was not a statistically significant association between use of powder in the genital area and ovarian cancer, but the study may have been underpowered to identify a small increase in risk."

The conclusions from O'Brien et al. brought two separate "Comment & Response" letters, one from Daniel Cramer, MD, ScD from Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, a physician-researcher and the primary author of first epi study on genital talc use and ovarian cancer in 1982.[72] In it, he highlighted concerns about the lack of frequency and duration data needed to assess a dose-response relationship, and casts doubt regarding recall bias as a potential explanation, noting differences in effect measures by histologic subtypes, and argues that talc use, likely a daily exposure, would be hard to forget.[73] He also notes his own work from 2016, which showed that the association between talc and ovarian cancer was stronger for premenopausal women who also used hormone replacement, suggesting the involvement of estrogen.[74] He concludes with in vitro evidence showing co-exposures of macrophages to talc and estradiol led to increased production of reactive oxygen species (ROS). Increased generation of ROS has been linked to DNA damage, which can lead to mutations and ultimately, carcinogenesis.

The second letter was from Bernard Harlow, PhD, Eleanor Murray, ScD, and Kenneth Rothman, Dr.Ph., of Boston University School of Public Health (Harlow and Murray) and Research Triangle Institute (Rothman).[75] Dr. Harlow is an epidemiologist with a focus on studies of female reproductive and gynecologic disorders, with expertise in methodology related to data collection. Dr. Murray is also an epidemiologist, with expertise in evidence-based decision making for public health and statistical and epidemiological methods for understanding causal effect. Dr. Rothman maintains his status as a Professor of Epidemiology and Medicine at Boston University and in addition to over 500 publications over the last several decades, he has written two books that are widely used to teach epidemiology: *Modern Epidemiology*, and *Epidemiology: An Introduction*. Their letter succinctly disagreed with the analysis and interpretation presented by O'Brien et al. and mentioned three distinct points. First, the lack of association seen in women without an intact genital tract, compared to one seen in women with an intact genital tract, should be considered curtailed exposure. Further, that although the statistical test for heterogeneity between the two groups was not statistically significant, "no statistical test is needed to know that women without an intact genital tract face a different risk of ovarian cancer than women whose genital tract is intact". The second point surrounded issues of bias and confounding that were not considered in the manuscript. Specifically, they propose that while the exposure likely started at younger ages but was assessed in the cohorts at a median age of 57, introduces a bias referred to as "depletion of susceptibles" meaning the women who developed ovarian cancer before the start of

the cohort would not be included. Other bias towards the null may have occurred because the confounding variables were assessed long after exposure started (per the Cramer study, around age 20) and the varying ways exposure was assessed across the studies could lead to misclassification. Finally, they note that relying on "statistical significance" based on a 95% confidence interval of 0.99-1.17 is now considered poor practice, and the hazard ratio of 1.13 should be taken as evidence of an effect.

The response by O'Brien et al. agreed with most points suggested by Dr. Cramer, including the fact that the cohorts have less detailed exposure information compared to case-control studies, that most women in the study were postmenopausal at enrollment, and they likely had misclassification of the exposure that bias findings towards the null.[76] They also note that the cohorts studies may be biased towards the null (pooled HR 1.08) and case-control studies may be biased away from the null (meta-OR=1.35) so perhaps the true association lies in the middle. They also completely agreed with the points made by Harlow et al., particularly regarding the point about intact vs non intact genital tracts. Hence, they agree that "that the positive association among women with patent reproductive tracts (HR, 1.13; 95%CI, 1.01-1.26) is consistent with the hypothesis that there is an association between genital powder use and ovarian cancer." This reverses the conclusion of the original manuscript that stated "there was not a statistically significant association between use of powder in the genital area and ovarian cancer".

In 2019, Taher et al. performed a meta-analysis of 27 studies, including 24 case-control and 3 cohort studies, to examine the association between ever use of perineal talc and ovarian cancer.[77] At the time of this writing, this is the meta-analysis that utilizes the largest amount of available data from epidemiologic studies. The summary odds ratio was 1.28 (95% CI: 1.20 to 1.37, nearly identical to the study by Penninkilampi and Eslick published the previous year.[78] They abstracted maximally adjusted estimates of risk from each study, and also used the Newcastle-Ottawa Scale for assessing the quality of the study. Pooled risk estimates were significant for serous tumors (OR: 1.38 (95% CI:1.22–1.56)), and endometrioid tumors (OR: 1.39 (95% CI: 1.05–1.82)) but not for the mucinous type (OR: 1.05 (95% CI: 0.85–1.29)) while other types of ovarian cancers were too rare to examine individually. Risk estimates were consistent for invasive and borderline tumors across subtypes. Risk was also examined by menopausal status and use of hormonal therapy, with postmenopausal women using hormones at highest risk (OR=2.28, 95% CI: 1.72-3.01), then premenopausal women (OR=1.42, 95% CI: 1.16-1.75), followed by postmenopausal women not receiving hormones (OR=1.05, 95% CI: 0.84-1.32). The relationship between use of postmenopausal hormones, perineal talc use, and ovarian cancer is important to follow, given the likely uptick in use again in the current generation of women undergoing menopause. Next, women who had undergone a tubal ligation showed a significant reduction in risk (OR: 0.64 (95% CI: 0.45 to 0.92)) for risk of ovarian cancer compared to those with a hysterectomy (OR: 0.89 ((95% CI: 0.54–1.46)) and both combined showed (OR: 1.06 (95% CI: 0.78–1.42)). Biologically, this may be explained as reducing exposure to talc when a tubal ligation is done at an early age (at the end of childbearing) versus a hysterectomy which is performed later in life. Lastly, authors note that the high degree of heterogeneity among the studies with respect to estimating cumulative exposure to talc precluded analysis in this meta-analysis. In addition to the epidemiologic studies, the authors included a summary of non-human studies, which will be discussed in section 10. They also applied the GRADE framework to assess the quality of the evidence for the meta-analysis, and it was deemed "Very Low". This is not surprising given the GRADE criteria includes randomized controlled trials as the highest level of evidence. As described in section 3, RCT are outside the scope of observational studies, and indeed, it would not be feasible to conduct one to test the association between perineal talc and ovarian cancer. Thus, the evaluation starts out as "low certainty" within the GRADE framework. Overall, the conclusions from Taher et al. were (as noted by the authors) similar to the Penninkilampi and Eslick meta-analysis from 2018 as well as the Berge et al. analysis (both described below).

In 2018, Penninkilampi and Eslick performed a meta-analysis of 26 case–control studies (13,421 cases and 19,314 controls) and 3 cohort studies (890 cases and 181,860 person-years) to examine the association between any perineal use of talc and risk of ovarian cancer. Overall, the summary odds ratio was 1.31 (95% CI: 1.24, 1.39) with higher estimates for >3600 uses (OR=1.42 (95% CI: 1.25, 1.61)).[78] Similar to Terry et al., increases in risk were identified for all types with the possible exception of mucinous cancers, where risk was increased but not statistically significant, and clear cell (which was likely underpowered as rare in ovarian cancers and only identified in 3 studies).[79] The same year, Berge et al. performed a similar analysis with nearly identical results with 24 case-control studies and the same 3 cohort studies.[80] This analysis discussed the differences in effect size between the case-control and cohort studies via a post-hoc power analysis, "It should be noted that the cohort studies included in the meta analysis comprised a total of 429 cases of ovarian cases exposed to genital talc and 943 unexposed cases: the statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case–control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as explanation of the heterogeneity of results." It should be noted that the WHI study alone contained 429 cases, so while the statement isn't completely correct, the point is the same. Power also depends on the variation of the prevalence of the exposure between cases and controls, but it is not described. Both analyses addressed publication bias, a type of bias only seen in meta-analyses. Both used a funnel plot and concluded based on visual and statistical assessment that their findings were not affected by publication bias.

In 2013, Terry et al. as part of the Ovarian Cancer Association Consortium (OCAC), published a pooled analysis of individual-level data for 8,525 cases and 9,859 controls from 8 population-based case-control studies that were part of the OCAC; 3 of these studies had not previously published their data regarding perineal talc and ovarian cancer risk.[79] Cases and controls were matched on study and age at diagnosis/study enrollment. Models were adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or 10+ years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other). The summary OR for ever versus never use of perineal talc and ovarian cancer was 1.24 (95% CI: 1.15 – 1.33) after adjustment. For the 6 studies that asked about both nongenital and genital use, estimates were higher for the genital use in each study. This analysis also included subtypes, with similar increases in risk seen for all types with the possible exception of mucinous cancers and the largest estimates seen for serous tumors. The authors did create a cumulative dose variable for studies with these details available. They reported similar increased risks of all nonmucinous subtypes of epithelial ovarian cancer combined across quartiles of genital powder compared with nonuse: ORQ1, 1.18; 95% CI, 1.02–1.36; ORQ2, 1.22; 95% CI, 1.06–1.41; ORQ3, 1.22; 95% CI, 1.06–1.40; ORQ4, 1.37; 95% CI, 1.19–1.58 (see Table 5). Although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis ($P_{trend} < 0.0001$), no trend in cumulative use was evident in analyses restricted to ever users (e.g. when the reference group was still exposed) $p_{trend}=0.17$. This might suggest a threshold effect associated with perineal talc use—that for some users a lower exposure is enough to cause disease. This study stands out as another pooled analysis, where individual-level data was analyzed. Thus, models could be adjusted for other potential confounding variables. In my opinion, the pooled analysis is a stronger approach versus other meta-analyses that use the risk estimate that had been previously published.

Muscat and Huncharek in 2008 published a review in the European Journal of Cancer Prevention and noted a summary relative risk of 1.3 (95% CI: 1.2,1.5) associated with use of perineal talc powders and ovarian cancer.[81] Their overall assessment is that cosmetic talc does not cause ovarian cancer, supported mostly by their assessment that it is unclear whether external talc enters the reproductive tract, and that talc that is not contaminated with asbestos is not carcinogenic. They note that the associations between talc-dusted diaphragm and condom use are null, but also mention that this may be due to use of other substances (i.e., contraceptive gels) and suggest more refined assessments of exposure in future studies.

The Muscat and Huncharek review was very similar to the findings by Langseth et al. in 2007.[82] This meta-analysis included 20 case-control studies, 14 of which were population-based (summary OR=1.4, 95% CI: 1.29-1.52) and 6 hospital-based (summary OR=1.12, 95% CI: 0.92-1.36) with an overall OR=1.35 (95% CI: 1.26-1.46). While not all studies were statistically significant, the authors note the "very large number of studies" have found that women who use talc have excess risk of ovarian cancer. In 2003, Huncharek et al. performed a meta-analysis of 15 case-control studies and 1 cohort study (all combined, 11,993 women) which reported a summary estimate of 1.33 (95% CI: 1.16-1.45) with ever vs never use.[83] The effect was weaker in hospital-based studies compared to population-based studies, and they did not detect a dose-response relationship. The discussion is a bit dated, as it notes that risk estimates below 2 are often dismissed by epidemiologists as uninterpretable. In my experience, training during the Genome Wide Association Study (GWAS) era, modest odds ratios are common, perhaps even to be expected, but not uninterpretable. This is also the first mention of the idea that the exposure was actually treatment-related, which was refuted later by Cramer et al. (2016) which reported average age at first use for cases and controls to be almost identical between cases and controls (20.0 and 19.8 years, respectively).

In 1995, Gross and Berg published the first meta-analysis to examine the association between perineal talc and ovarian cancer.[84] The study was comprised of 9 case-control studies and 1 cohort study published between 1982 and 1993. While the sample sizes for each individual study were relatively small (most around 200 cases and 200 controls), the meta-analysis overall reported a relative risk associated with ever use in 8 studies (those that had adjusted measure of effect) of 1.31 (95% CI: 1.08,1.58) in all tumor types. When limiting to just epithelial tumors (and only 5 studies) risk was essentially the same (RR=1.29, 95% CI: 1.02, 1.63). Ultimately the authors concluded that the meta-analysis did "suggest the possibility of increased risk of ovarian cancer due to perineal talc use" and that further study was needed. This work was supported in part by Johnson & Johnson.

Table 3: Meta-analysis examining the association between perineal talc use and risk of ovarian cancer

Study (year) (ref)	Overall Measure of Effect (95% CI)	Number of studies included	Exposure measurement
Phung et al. (2022)[85]	1.38 (1.04,1.84) 1.12 (1.01,1.25)	9cc	Any (Endometriosis) Any (no endometriosis)
Woolen et al. (2022)[71]	1.47 (1.31,1.65)	10cc; 1 cohort	Multiple times per week or more
Davis et al. (2021)[86]	1.22 (0.97-1.53) 1.36 (1.19,1.57)	4 cc, 1 nested cc	African American women White women
O'Brien et al. (2020)[87]	1.13 (1.01,1.26)	4 cohort	Any (patent tract)
Taher et al. (2019)[77]	1.28 (1.20,1.37)	24 cc; 3 cohort	Any
Penninkilampi and Eslick (2018)[78]	1.31 (1.24,1.39)	26 cc, 3 cohort	Any
Berge et al (2018)[80]	1.22 (1.13,1.30)	24 cc; 3 cohort	Any
Terry et al. (2013)[79]	1.24 (1.15,1.33)	8 cc	Any
Muscat and Huncharek (2008)[81]	1.30 (1.2,1.5)	20 cc	Any
Langseth et al. (2007)[82]	1.35 (1.26,1.46)	20 cc	Any
Huncharek et al. (2003)[83]	1.33 (1.16,1.45)	15cc; 1 cohort	Any
Gross and Berg (1995)[84]	1.31 (1.08,1.58)	9 cc; 1 cohort	Any

As shown in Table 3, the meta-analyses were consistent in reporting a positive association between ever versus never perineal talc use and ovarian cancer (and higher for the frequency of use analysis by Woolen et al). This is not entirely surprising, as each newer meta-analysis contains the studies examined in the earlier meta-analyses, in addition to more recent publications. The pooled analyses with individual-level data all also supported a positive association between perineal talc use. Taken

together, these meta-analyses containing studies from a large number of geographically diverse areas provide strong evidence supporting an association between perineal talc and ovarian cancer.

iii. Other types of reviews

In addition to the government-sponsored reviews, there have been several recent publications that do not include novel data collection or analysis. I tend to put less weight on these reviews, particularly if they are not "Invited Reviews" (invited by the journal editor) and if they are performed by a small number of investigators or investigators from the same organization. Commentary or Letters to the Editor that are in direct response to a published report (containing novel data or data analysis) are described when discussing the original manuscript. The final section includes statements or information from cancer foundations or professional groups.

Invited

I only identified a single *invited* review, published in 2021 in Gynecologic Oncology, a top specialty journal. Drs. Wentzensen and O'Brien, with the National Cancer Institute and the National Institute of Environmental Health Science, respectively, provided a summary that included a discussion of the chemical properties of talc in body powder, the biological properties of talc and carcinogenicity, epidemiologic studies (including strengths and weaknesses of study design, biases, etc.), findings stratified by histologic subtype, tubal ligation and hysterectomy status, and race and ethnic groups.[88] They also examined the limited data examining talc use and endometrial cancer. Focusing on the bulk of their review, which was the discussion of epidemiologic studies, I took away the following:

•"Overall, these results consistently demonstrate that there is a positive association between talc use and serous ovarian cancers, and possibly also endometrioid tumors."

•"However, the results of the prospective studies support the hypothesis that the positive association between genital powder use and ovarian cancer may be limited to women with patent reproductive tracts."

•Effect estimates are similar between non-Hispanic white women and African American women, and African American women were more likely to report talc use.

In their conclusion, they note that it is difficult to differentiate between types of powders used, although talc is a major component in many powders. They mention the lack of animal or experimental models currently available, and ultimately note that there is a lack of understanding of "the causal factors that underly the observed weak associations between genital powder use and ovarian cancer".

This invited review drew a response from Dr. Cramer, a noted physician-scientist from the Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School who published the first case-control study examining talc and ovarian cancer and remains active in the field.[73] He highlighted the issue of recall bias in the study by Schildkraut et al. and gave a detailed description as to other explanations. Additionally, he highlighted a number of recent experimental studies that addressed the concerning lack of experimental models available, including a study that, "exposed human ovarian cancer cells and normal fallopian tube cells to talc and found significant increases in markers of inflammation and cell proliferation to a greater degree in the normal compared to the cancer cells" and another that looked at the combined effects of talc and estradiol on macrophages (a marker of inflammation). Overall, his comments added additional information that was lacking in the original review, and his comments regarding recall bias were particularly insightful, and are included later in this document when discussing specific case-control studies.

Investigator-initiated

In 2023, Lynch et al. published a review examining the association between talc and female reproductive cancers. With the exception of Dr. Paolo Boffetta, all are employees of Stantec

(ChemRisk), a for-profit company with services across multiple sectors, including environmental health risk assessment. Dr. Boffetta is a Senior Advisor to ChemRisk, it is unclear if this is a compensated role. The lead author is a MPH-level researcher whose scientific work is focused on reviews. They conclude that there is "insufficient evidence to conclude with any confidence that there is a causal connection" based on lack of consistency of a dose-response relationship, and what they deemed as "low-quality" ratings for exposure characterization and risk of bias.

In 2022, a commentary by Micha et al. was published in the Archives of Gynecology and Obstetrics "News and Views" section, which offered the vague conclusion, "…researchers should further evaluate the effects of both prolonged exposure and specific timing (i.e., opportunistic circumstances) of talc use to conclusively determine if the silicate harbors carcinogenic potential." That same year, the meta-analysis by Woolen et al. did look at frequency and duration of exposure, limiting the study to those with usage of at least twice a week, reporting the largest measure of effect of all meta-analyses (OR_{meta}=1.47 (1.31, 1.65), although this was not mentioned in the commentary. The authors are board members of the Women's Cancer Research Foundation, and the work was supported by gifts to this nonprofit. This review presented no new data or analyses and failed to reference at least two dozen epidemiologic studies. Other than an opinion piece it is unclear what this adds to scientific knowledge about the association between perineal talc exposure and risk of ovarian cancer. Tran and Egilman published a response to this commentary noting the following ways the response was flawed: 1. Asbestos is not just "notoriously associated with malignancies" but has been directly implicated in ovarian cancer; 2. The causal link between asbestos and ovarian cancer extends to cosmetic talc, because talcum products contain asbestos; 3. Key pieces of evidence establishing a causal link were not included; 4. Evidence for transmigration does exist, including an analysis J&J did independently; 5. If recall bias were to occur one would expect to see it across all histologic groups and studies that have the ability to examine this do not find risk across all subtypes; 6. Evidence exists that p53 mutations are associated with asbestos, and occur in 80% of serous ovarian cancers.[89]

In 2020, four investigators from Gradient, an environmental health firm with offices in Boston and Seattle, published a review of talc and ovarian cancer in the Journal of Toxicology and Environmental Health, Part B, which publishes reviews.[90] This work was funded in part by the Cosmetic Alliance of Canada and the Industrial Mineral Association of North America. It was a comprehensive review, including an assessment of biologic plausibility (mainly from animal and *in vitro* studies). From an epidemiologic viewpoint, they focused almost exclusively on statistical significance, and bias. Some of the suggestions to mitigate recall bias are not feasible, such as "using objective measures of talc exposure instead of reported exposure…" It is not clear what this objective measure would be. Similarly, they note that asking about a variety of exposures also reduces recall bias and highlight one paper that only asked about talc (and cigarette smoking). This is a misrepresentation of the questionnaires—most contain data on a wide variety of exposures, including reproductive and medical histories, family history, diet, exercise, cigarette smoking, alcohol use, medication use, etc. The concerns about bias and confounding described tend to be general concerns in the field, and not necessarily specific to talc exposure. I would also note that this may be due to the fact that these investigators do not have extensive histories of performing novel research including data collection from participants.

Professional Organization and/or Foundation Statements for Patient Care

My searches also identified several websites or press releases from professional organizations or foundations. It was unclear what, if any, methodology was used to support their recommendations. While I did not put much weight onto these statements, I include them here for completeness.

American Cancer Society (last revised: December 6, 2022): “Studies of personal use of talcum powder have had mixed results, although there is some suggestion of a possible increase in ovarian cancer risk.”[91] The website also notes: “The US National Toxicology Program (NTP) is an interagency program of several different government agencies, including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). The NTP has not fully reviewed talc (with or without asbestos) as a possible carcinogen.”

American College of Obstetricians and Gynecologists (ACOG) (2017): “Because of concerns regarding potential discomfort or pain, obstetrician-gynecologists do not recommend use of vaginal treatments such as douche, vaginal sprays or talcum powder and the use of talcum powder has declined over the years. There is no medical consensus that talcum powder causes ovarian cancer.”[92]

National Academy of Science (formerly referred to as the Institutes of Medicine) released a report in 2016 and discuss perineal use of talcum powder with respect to the causal association between asbestos and ovarian cancer. They then state, “This has led to studies of talc use, which is chemically similar to asbestos and can cause an inflammatory response. The use of perineal talcum powder has been associated with a 20 to 30 percent increased risk of ovarian cancer, although it also has been show to vary by histologic subtype (Cramer et al., 2015; Terry et al., 2013).”[93]

NCI: Ovarian, Fallopian Tube, and Primary Peritoneal Cancers Prevention (PDQ®)–Health Professional Version (updated October 16, 2023): “Results from case-control and cohort studies are inconsistent, so the data are inadequate to support an association between perineal talc exposure and an increased risk of ovarian cancer.” No changes were made to this section since the last update. It should be noted that, “The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).”[94] This reference section includes only 7 references related to perineal talc exposure.

X. Cohort studies

Cohort studies are generally best to study relatively common diseases and also have the advantage of allowing for more than one outcome of interest in a single study. If the study participants are disease-free at baseline and exposure data is collected at that time, temporality of the association between the exposure and disease is clearly established. A disadvantage to the cohort design, in addition to the cost of following the participants (and the potential loss to follow up) is that even the largest studies accrue fewer cases than a case-control study, and the risk factor assessment is often less detailed, particularly if the disease of interest is not the primary endpoint of the study.

There are only three prospective cohort studies that have presented novel data examining the association between perineal talc exposure and risk of ovarian cancer. Data from the Nurses’ Health Study II (n=76 cases) are available in the meta-analysis by O’Brien et al., as are updated data from the other studies: Sister Study, Women’s Health Initiative, and the Nurses’ Health Study. In 2024, O’Brien et al. released an updated analysis of the Sister Study data, including an extensive methodological study of misclassification and recall bias. I examined each study in detail, noting the overall measure of effect and 95% confidence interval, how the exposure was categorized, the percent of the cohort exposed, the overall size of the cohort, the number of cases to date, and the year the recruitment started. When available, I included median follow up time. The findings from the individual studies are described below and summarized in Table 4.

In 2024, O’Brien et al. examined various intimate care products, including genital talc, and risk of breast, uterine and ovarian cancers in an updated analysis containing n=292 ovarian cancers, nearly twice the number in the original report (n=154).[95] The authors noted that douching increased risk of ovarian cancer, mostly among long-term users (more than 2 decades) and frequent users, although associations are also associated with ever/never use. The majority of the analysis in this manuscript

focused on the association between genital talc use and ovarian cancer, as outlined below. Of note, genital talc was not associated with uterine or breast cancers, but was associated with ovarian cancer, with risk estimates similar to what has been reported in other studies. This article additionally performed a detailed statistical examination of these data to explore the potential impact of misclassification of exposure at different time points, as well as overreporting of the exposures. For nearly every scenario, the association between genital talc use and ovarian cancer persisted, leaving the authors to conclude, "Overall, our findings support the hypothesis that there is a positive association between genital talc use and ovarian cancer incidence…" and then go on to correctly note that this analysis does not pinpoint a specific underlying mechanism.

For assessment of misclassification of the exposure, the authors provide a detailed assessment describing different scenarios in reporting, essentially creating estimates for misclassification of genital talc use. They considered various inaccuracies in the classification of genital talc use at enrollment and/or at follow up, by those who were exposed and unexposed. In this analysis, even with a large portion of the study population misclassifying exposure, the association between genital talc use and ovarian cancer still exists. In every scenario, ever use of genital talc is associated with increased risk (HR range from 1.07 to 3.34). Use of imputation, a standard statistical method used to predict what a missing response would be based on information from similar respondents without missing data, demonstrated genital talc use was still associated with ovarian cancer (HR=1.82, 95%CI: 1.35, 2.43).

For the recall bias assessment, if 50% of cases who reported exposure were in fact not exposed, there remained a positive association between genital talc use and ovarian cancer (HR=1.07, 95% CI: 0.82, 1.40). This persisted at lower rates of recall bias (25% and 10%), but not at the highest rates (75% and 90%). It seems unlikely, given the multiple studies and years of use of genital talc generally reported by users, that 75% or more of women would overreport to this extent. Additional analyses examining the change in estimates of association between women with ovarian cancer reporting infrequent or short term use showed positive associations even if 90% of women were reassigned to never use. Similarly, if noncases who reported never use were reassigned to being short term or infrequent users, even a 25% reassignment garnered a positive association between genital talc use and ovarian cancer.

The association between genital talc use and ovarian cancer remained, and were slightly larger, in an analysis restricted to women with patent reproductive systems, even after assessment for misclassification and recall bias. Furthermore, they were able to examine these data by timing of use in decades, which allows consideration of windows of susceptibility, when a person may be more susceptible to the effects of an exposure. Overall, without correction and utilizing imputation, the estimates between ever genital talc use and ovarian cancer indicate women who ever used genital talc have an 82% increase in risk compared to those who never used (HR=1.82, 95% CI: 1.35, 2.43), which is attenuated to a 40% increase in risk once corrected for recall bias (HR=1.40, 95% CI: 1.04, 1.89).

To date, this is the most thorough analysis of bias examining the association between genital talc use and ovarian cancer. The strong, well-reasoned methodology accounts for potential biases that have been considered potential explanations for the positive associations seen in observational studies. Notably, the consistency of the positive association between genital talc use and ovarian cancer remained regardless of the various scenarios presented with respect to overestimating exposure among cases, misclassification of exposure at various timepoints, and imputation of missing data. Missingness was more common amongst the cases, which is unsurprising given the aggressive and highly fatal nature of ovarian cancer. While there is always the potential that there are other, unknown factors that may confound the relationship between genital talc use and ovarian cancer, it is unlikely. After decades of studies in various populations and different investigators across the globe the data reveal strikingly similar estimates of association.

An editorial accompanied the analysis by O'Brien et al. and noted that after the detailed assessment

and variety of methods used to address misclassification and recall bias there was a significant increase in ovarian cancer risk associated with genital talc use, of a magnitude similar to what has been reported in previous studies.[96] The authors note that this methodologically sound analysis finds that, "…a significant increase in ovarian cancer risk is still observed, adding support to the plausibility of a true association between genital powder use and ovarian cancer risk." Additionally, they conclude that given the fact that talc is a modifiable risk fact—"likely associated with a highly fatal disease"—that people at risk of ovarian cancer should be made aware of the potential risks associated with use.[96]

In 2016, Gonzalez et al. presented an analysis of the association between talc use and risk of ovarian cancer among participants in the Sister Study in 2016.[97] This study enrolled and followed 50,884 women from 2003-2009 and talc use over the last 12 months was ascertained at baseline. Enrollees were aged 35 to 74 years and had never had breast cancer but each had a full or half-sister who had been diagnosed with breast cancer. After excluding women with bilateral oophorectomies or ovarian cancer at baseline, there were 41,654 participants, with 154 ovarian cancers observed (median follow-up time 6.5 years). Overall, there was no association between talc use in the past 12 months and risk of ovarian cancer (HR=0.73, 95% CI: 0.44-1.2) after adjustment for race, body mass index, parity, duration of oral contraceptive use, menopause status, and patency. No associations were seen when stratified by patency, hysterectomy, tubal ligation, parity or menopause status. It should be noted that the time limit given for talc use (within the last 12 months) reduced the percentage of women who used talc, with only 14% reporting use (see below and Table 4 for other studies). This suggests there may be non-differential misclassification of the exposure, which in this case would drive the risk towards the null. After publication of this report, the Sister Study asked about use between ages 10 and 13 years, with these data included in the O'Brien et al. 2020 meta-analysis, bringing the ever use to 27%. This provides evidence that the 14% in the Gonzalez et al. analysis did indeed have misclassification of the exposure.

In 2014, Houghton et al. examined perineal powder use and risk of ovarian cancer among participants in the Women's Health Initiative Observational Study, which enrolled women from across the United States from 1993-1998.[98] There were 61,576 postmenopausal women available for analysis after exclusions for prior cancer, bilateral oophorectomy (or unknown), or missing follow up or exposure information. There were 429 women with incident ovarian cancers during the (mean) 12.4 years of follow up. Over half of the women (52.6%) reported using perineal powder. Focusing on perineal use, the hazard ratio associated with ever use and risk of ovarian cancer was 1.12 (95% CI: 0.92 to 1.36) after adjustment for age, race, years oral contraceptive use, years hormone replacement therapy use, family history, age at last birth, body mass index, smoking, tubal ligation and parity. This analysis contained details regarding where or how the powder was used, with the largest association seen for those who reported both genital and diaphragm powder use (HR=1.49, 95% CI: 0.98-2.28) but this only represented n=24 cases. The most common use was "only genital powder" with n=96 cases and HR=1.14, (95% CI: 0.90-1.46). Restriction to women without tubal ligation did not change estimates, nor was a dose response relationship identified (although this was limited to years of use, not number of applications, classified as less than 9 years or greater than or equal to 10 years). Adjusted hazard ratios stratified by subtype ranged from 1.03-1.16; none were statistically significant but were all likely underpowered to detect an association below 2.0.

In 2010, Gates et al. published an analysis examining various risk factors for ovarian cancer by histologic subtype, combining data from both Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II).[99] The NHS was established in 1976 and recruited 121,700 female registered nurses aged 30-55 years. Talc use was ascertained in 1982 in a self-administered follow up questionnaire as greater than or equal to once a week or less than once a week. NHS II was established in 1989, recruiting 116,430 US female registered nurses aged 25–42 years. A combined total of n=797 cases were identified, with n=670 from NHS and n=127 from NHS II; however, NHS II did not collect information on talc at baseline and thus was not included in the talc analysis. For all epithelial cancers, they reported a relative risk of 1.06 (95% CI: 0.89, 1.28) after adjustment with approximately 24 years of follow

up.The estimates were the same for serous and endometrioid, and larger for mucinous (RR=1.50, 95% CI: 0.84, 2.66) although the case numbers for mucinous were small (n=84). The overall estimate differed slightly from the first report using NHS data in 2000 but was within the same range. Note that there are differences in how exposure is classified between the two studies, with the 2010 data grouping those with less than one a week usage into the referent group. This potentially introduces differential misclassification, which in this case could biases the measure of effect towards the null.

The first prospective data regarding perineal talc use and ovarian cancer was reported by Gertig, et al. in 2000, using data from the Nurses' Health Study (NHS).[100] This report contained 307 epithelial ovarian cancers that were confirmed by medical record review from 78,630 eligible women. Ever use of perineal talc was reported by 40.4% of participants, with a relative risk of 1.09 (0.86–1.37) for ever users compared to never users. Using talc on perineum or on sanitary napkins resulted in a relative risk of 1.15 (95 % CI: 0.9-1.46) after adjustment for age, parity, duration of oral contraceptive use, body mass index, tubal ligation history, smoking status, and postmenopausal hormone use. When stratified by histologic subtype, risk was increased for serous invasive cancers (RR=1.40, 95% CI: 1.02-1.91). In this group, the p-value for trend of number of times per week used was 0.05. While the number of cases and follow up time is limited, authors noted that perineal talc use may modestly increase the risk of invasive serous ovarian cancers.

Table 4: Cohort studies examining the association between perineal talc use and risk of ovarian cancer

Study (year) (ref)	Overall measure of effect (95% CI)	Exposure (% exposed)	Study/n/cases (year recruitment started)	Notes
Gertig 2000[100]	1.09 (0.86–1.37)	Ever/never (40.4%)	NHS/78,630/307 (1976)	NHS asked in 1982, Invasive: 1.40 (1.02, 1.91); p_{trend} for times per week=0.05
Gates 2010[99]	1.06 (0.89, 1.28)	≥1 per week/<1 per week (not reported)	NHS/108,073/797 (1976)	NHS II did not collect talc
Houghton 2014[98]	1.12 (0.92, 1.36)	Ever/never perineal (52.6%)	WHI/61,576/429 (1993)	12.4 years of follow up
Gonzalez 2016[97]	0.73 (0.44, 1.2)	Ever/never (14%)	Sister/41,654/154 (2003)	Asked ages 10-13 and last 12 months only
O'Brien 2024[95]	1.40 (1.04, 1.89) after correction estimate of 25% of exposed and 10% of unexposed reassigned	Ever/never (35%)	Sister/40,536/292 (2003)	Updated from Gonzalez, included age at first and most recent use, frequency of use by decade

In summary, both the WHI and the NHS report similar, positive associations with use of perineal talc and risk of ovarian cancer. The original Sister Study publication did not, which may be due to misclassification of the exposure (only last 12 months) with only 14% of cases originally reporting talc use in the last 12 months.[97] The updated pooled analysis by O'Brien et al. included talc use at younger ages (10-13 years) and found the usage increased to 27%. Given that both WHI and NHS reported 52.6% and 40.4%, it is unclear whether 27% is still an underestimate, or if personal habits have changed somewhat over time. In the most recent update of the Sister Study cohort, the most

contemporary cohort with respect to the timing of the recruitment, a detailed analysis reported a positive association between genital talc exposure and ovarian cancer, similar in magnitude to estimates reported in case-control studies.[95]

XI. Case-control Studies

Case-control studies are warranted when the disease of interest is relatively rare as it allows the accrual of a large number of cases in a fraction of the time (compared to cohort studies) and the ability to ask more detailed questions about potential exposures. Since the first study in 1982, over 20 other case-control studies have been published in peer-reviewed journals. As shown in Table 5, the majority of these studies reported an association between use of perineal talc and ovarian cancer. Below I provide a brief overview by study, focused on publications from the year 2000 forward, which have larger sample sizes, making it feasible to perform stratified analyses (e.g., by tumor subtype) and examine dose-response.

In 2016, the most recent case-control study published was by Cramer et al. with 2,041 cases and 2,100 controls from Eastern Massachusetts and New Hampshire, with cases identified via population-based registries and controls identified via random digit dialing, driver-license lists, and town-resident lists.[74] Approximately 71% of cases and 54% of controls participated in the study. Genital talc use was defined as regular application to the genital/rectal area directly, on sanitary napkins, tampons, or underwear. An estimate of duration and frequency was created by multiplication of the number of applications per year by years used. For ever versus never use, the odds ratio was 1.32 (95% CI: 1.15, 1.51), after adjustment for age, study center, and phase. A dose-response pattern was noted, with women who used perineal talc daily for 20 years being nearly 50% more likely to have ovarian cancer compared to women who did not use talc (OR=1.49, 95% CI: 1.06, 2.10), with the p-value for the trend between the duration categories of 0.02 for women with complete data for both use and duration variables.

In this analysis, confounding and effect modification are also examined, with an entire table (Table 2) dedicated to the analysis. In short, the factors examined did not appear to modify or confound the association between perineal talc and ovarian cancer. Additionally, this manuscript has a detailed discussion of recall bias. To quote: “(1) ORs are generally lower in studies which asked about “ever use” of talc compared with those that specified regular use, whereas higher ORs would be expected if cases are more likely to recall limited ever-use; (2) no association with nongenital talc use; (3) risk varies by histologic type; (4) the association is stronger in premenopausal women who are closer in time to talc use and less likely to have forgotten it; and (5) ORs from recent studies are lower than those from earlier ones, whereas increasing publicity about the association over time might lead to greater recall bias and higher ORs in more recent studies.” I am in agreement with this explanation. The authors also note that if there was misclassification of the exposure, it would have to be at least 18% to nullify the association between use of talc on genitals and ovarian cancer risk in this study.

Also published in 2016, the study by Schildkraut et al. was focused on African American women with ovarian cancer.[1] There were 584 cases and 745 controls available for the analysis from the African American Cancer Epidemiology Study (AACES). Starting in December 2010, cases and controls were identified from 11 different sites, and controls were identified via random digit dialing. No participation rates were provided as the study was ongoing. Exposure was determined by asking whether participants had ever regularly used talc, cornstarch, baby, or deodorizing powders. Participants were considered "regular users" if they reported using any of these powders at least one time per month for at least 6 months, and "never users" if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or nongenital areas. The odds of having ovarian cancer were 44% higher among genital talc users compared to non-users

(OR=1.44, 95% CI: 1.11, 1.87) and were also elevated for those who reported only non-genital use (OR=1.31, 95% CI: 0.95–1.79). Talc use was higher than what was reported in prior studies, with more cases reporting talc use (42.5% genital only, 20.4% non-genital) than controls (34.1% genital only, 18.8% non-genital). Dose-response was also noted, with higher risk for those with more than 3,600 lifetime applications (OR=1.67, 95% CI: 1.23–2.26) compared to non-users, and still elevated for those with fewer than 3,600 lifetime applications (OR=1.16, 95% CI: 0.83–1.63). This dose–response relationship was not seen with frequency, duration, or lifetime applications of "only" nongenital powder use.

This is the only case-control study to date that directly attempts to assess recall bias. There are several ways that recall bias may be introduced into a study. First, if the exposure of interest is one that could be considered sensitive (e.g., illicit drug use, history of sexually transmitted infections) there may be hesitation to answer accurately. For talc use, while it may not be widely discussed, it is unlikely to be a sensitive subject. Additionally, usage patterns and reliability of self-reported data on douching and genital talc use was examined in participants from the Sister Study. Respondents could recall use of these products with good consistency.[101]

Next, if the study hypotheses are known to the subjects or interviewers, it may alter the way questions are asked by the interviewer (additional probing of cases, compared to controls, for example) or answered by the subjects. Given that this study, along with nearly all other case-control studies, ask an abundance of questions related to health history, family history, “healthy” behaviors (i.e., diet, physical activity), reproductive history, medication use, etc. it is unlikely that talc would have been answered differently than any other factor. There is no second source to check for confirmation of talc use. Also, most studies, including AACES, “double-blind” participants and interviewers about the aims of the study. The interviewers also often don’t know if they are contacting a case or control, unless the participant discloses this information.

Finally, recall bias could be introduced if there has been media attention focused on the exposure. This is the point the authors attempt to address by dividing the population by interview date, centered around 2014, with respect to the potential increase in public awareness regarding talc use and ovarian cancer risk. As the study population was recruited starting in 2010 and continued through 2015, this cohort could be split into “before” and “after”. This is not a concern for other case-control studies, as they collected data prior to the time when the first lawsuits (and the publicity surrounding them) were filed in 2014—many decades before this time.

In Schildkraut et al., Table 2 shows that the percentage of cases reporting of any genital use went from 36.5% among the cases interviewed prior to 2014 to 51.5% in cases interviewed after 2014. Nongenital use was relatively stable among cases prior to 2014 (20.4%) and after 2014 (18.4%). For controls, reported non-genital use increased from 17.6% to 23.3% in prior to 2014 vs after 2014, respectively, but genital use remained the same among controls (34.0% and 34.4%, respectively). Correspondingly, the OR for any genital use prior to 2014 interview was (OR=1.19, 95% CI: 0.87, 1.63) and higher for those reporting post-2014 (OR=2.91, 95% CI: 1.70, 4.97). This indicates the possibility of some level of recall bias, but it should be noted that the OR of 1.19 is well-within the range of estimates reported by other studies. Thus, the results attenuated, but did not eliminate, the association between genital talc and ovarian cancer.

There are other possible explanations to consider, as pointed out by Dr. Cramer in his response to the O’Brien report.[73] Specific to the issue of recall bias in the AACES study, he draws from other data about talc use reported by African American women. Specifically, he suggests that talc use was actually “erroneously underreported” by cases before 2014, versus “erroneously over-reported” by cases after 2014 and notes that in his studies, 54% of African American women reported genital talc use compared to 26% of the controls—all prior to 2014. Another study by Wu et al. in 2015 (see below)[103] also prior to

2014 reported 48% of African American women with ovarian cancer used talc. Both of these usage rates are higher than the 36.5% among cases reported in AACES.

In 2015, Wu et al. published a study with findings stratified by race and ethnicity. This was an update of the study population first analyzed in 2009.[102,103]This included 1265 non=Hispanic white cases and 1868 non-Hispanic white controls, 308 Hispanic cases and 380 Hispanic controls, and 128 African American cases and 143 African American controls. Cases were identified through the Los Angeles County SEER Program from 2003 through 2008. Participation rates for cases were listed as 61.1% for non-Hispanic whites, 76.1% for Hispanics, and 59.8% for African Americans. Controls were identified through a neighborhood algorithm to and individually matched to cases on year of birth and race and ethnicity, although controls were identified by using lists of female residents of Los Angeles County provided by the Health Care Financing Administration, matched to the case on zip code, race/ethnicity, and year of birth closest to the case's year of birth. Seventy percent of the controls were the first control selected. Exposure to talc was ever/never, with those reporting use of less than 1 year as never. Talc use was more common in African American women (44.1%) than in non-Hispanic whites (30.4%) or Hispanics (28.9%; p-value=0.001).

Overall, the goal of the Wu et al. analysis was to evaluate differences in risk across non-Hispanic whites, Hispanics, and African Americans. Authors "…investigated only the six factors that are confirmed, noncontroversial, showing strong associations with all invasive ovarian cancers in non-Hispanic whites." Talc was one of the risk factors examined, and no notable differences were seen by race and ethnicity, with the OR's ranging from 1.41 (95% CI: 1.21, 1.67) in non-Hispanic white women, 1.77 ((95 CI: 1.20, 2.62) in Hispanic women, and 1.46 (95% CI: 1.27, 1.68) in African American women. Dose-response was also noted, with risk increasing ~14% for every five years of use.

In 2012, Kurta et al. published their case-control study that was primarily focused on the association between fertility treatments and risk of ovarian cancer.[104] Their study population consisted of 902 cases and 1,802 controls from Western Pennsylvania, Eastern Ohio, and Western New York State as part of the Hormones and Ovarian Cancer Prediction (HOPE) study that recruited cases from 2003-2008. Controls were frequency matched to cases (2 controls per case) by 5-year age group and telephone area code and identified via random digit dialing. Participation rates for cases and controls were not provided. Exposure to talc was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps. An association between talc exposure and ovarian cancer was reported (OR=1.40, 95% CI 1.16, 1.69) after adjusting for age, race and education. As talc exposure was not the focus of this report, there was limited discussion about this finding.

In 2011, Rosenblatt et al. recruited 812 cases (595 had invasive disease) identified through the population-based Surveillance, Epidemiology and End Results registry that covers residents in 13 counties in Washington.[46] Cases were recruited from January 2002 through December 2005, with a response rate of 76.6%. Controls were identified via random digit dialing (RDD) based on 5-year age group and county of residence. The case participation rate was reported to be 76.6%, and the control participation rate was 69%. The exposure assessment for talc was detailed [the following taken directly from the manuscript], "including direct perineal application after bathing, its use on sanitary napkins and contraceptive diaphragms, and the use of feminine (vaginal) deodorant spray. For powder use on sanitary napkins and use of feminine deodorant sprays, the total number of months or years in which these products were used (with a minimum of at least 1 month of regular use). For the use of powder on the perineum after bathing, only intervals of at least 1 year when powder was usually used were recorded. For each reported interval in which powder was usually used on the perineum after bathing, we recorded the age when began and ended, the number of weeks or months of use per year, and the average days per week used. Women were also asked to report the types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The extent of

exposure to perineal powder after bathing was assessed as lifetime duration of use (i.e., total number of years in which this exposure occurred), and as the estimated lifetime number of applications (i.e., a measure that incorporated both the duration and frequency of use)." It should be noted that the participants were given calendars to record major life events to aid in recall.

The use of powder after bathing (for at least 1 year of regular use) was the most commonly reported exposure, but still relatively rare compared to other studies, with 12% of controls reporting use. Overall, the perineal use of powder after bathing was associated with increased risk (OR = 1.27, 95% CI: 0.97–1.66), which was slightly higher among women with borderline tumors (OR = 1.55, 95% CI: 1.02–2.37). When combining all types of exposure, the risk of invasive ovarian cancer among women who reported the use of talcum powder was 1.38 (95% CI: 0.77–2.47). Use only on diaphragms did not appear to be associated with risk across all subtypes, but numbers are small. A dose-response effect was also not identified. The most commonly reported powder used was baby powder. Authors noted that use of pure cornstarch powder was quite uncommon in this study; if this information is accurate (and extends to other populations), then measures of genital powder use of any type may be a reasonable surrogate for talc exposure.

Also in 2009, Moorman et al. recruited cases and controls from North Carolina.[105] The aim of the manuscript was to compare risk factors for ovarian cancer between white and black women. They recruited 746 white women with ovarian cancer, 111 black women with ovarian cancer, 868 white controls and 189 black controls. Talc use was not defined in the methods and was only presented in Table 3. Of note, talc responses were missing for 32% of the study participants overall (614/1914) and other than the presentation of the odds ratio associated with use, there was no further discussion offered in the manuscript.

In 2008, Gates et al. performed a gene-environment study examining the effects of perineal talc and genes in the detoxification pathway (*GSTM1*, *GSTT1*, and *NAT2*) with risk of ovarian cancer.[104] They recruited 1,175 cases and 1,202 controls from a New England-based case-control study and a nested case-control study was created from 210 cases and 600 controls in the prospective Nurses' Health Study. For the case-control study, 71% of the eligible cases were enrolled in the study. Controls, identified via random-digit dialing, drivers' license records, and Massachusetts' town resident lists, were frequency matched to cases by age and state of residence. Of the potentially eligible controls contacted 68% were eligible and agreed to participate.

The case-control study asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear, or nongenital areas), frequency of use, age at first use, number of years used, and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, less than once a week, 1-6 times a week, or daily) or to sanitary napkins (yes/no). For this analysis, regular genital talc use was defined as application of powder to the genital/perineal region at least once a week. A categorical variable for frequency of talc use was created using the categories from the NHS.

The results addressing the primary aim of the study suggest that genes in detoxification pathways may be involved in the biological response to talc and that the association between genital talc use and risk of ovarian cancer may vary by genotype. In particular, women with the GSTT1-null genotype and the combined GSTM1-present/GSTT1-null genotype had a stronger association between talc use and ovarian cancer risk. Authors note that the direction of the association was not in line with what they expected, and that future work would be necessary to confirm findings. No other studies to date have examined this potential gene-environment interaction. None of the genetic variants selected for study were associated with ovarian cancer. This study did find that ever/never use was associated with ovarian cancer after adjustment (RR=1.36 (95% CI:1.14-1.63), and the trends for use, both frequency and duration, supported a dose-response relationship (p-trends <0.001).

In 2008, Merritt et al. published a case-control study from Australia. Women with invasive and low malignant potential ovarian cancer diagnosed (aged 18–79 years) between January 2002 and June 2005 were included, 2,319 (84%) agreed to take part.[107] After pathologic review, 1,685 eligible participants were identified, and 94% participated (final n=1,576). Controls were frequency-matched to the entire case series based on age (5-year groups) and state of residence, 47% of those approached participated (n=1,509). Participants were asked whether they had ever used powder or talc in the genital area or on underwear or sanitary pads/diaphragm. Age at first use and years of talc use in these areas was also queried. Duration of talcum powder use prior to and after hysterectomy/tubal ligation was calculated and in all analyses perineal talc use was defined as use occurring while the reproductive tract was patent (i.e., prior to hysterectomy/tubal ligation for those women who had undergone gynecological surgery). Information on talc use under the arms or on the chest or abdomen was also collected.

Ever use of talc in the perineal region (among women with patent fallopian tubes) was associated with a significant increase in risk of all types of epithelial ovarian cancer combined (adjusted OR= 1.17, 95% CI: 1.01–1.36); risk remained when stratified by serous and endometrioid subtypes (adjusted OR=1.21, 95% CI:1.03–1.44 and 1.18, 95% CI 0.81–1.70, respectively). Talc use on other body sites showed no association. Additionally, associations were only identified in women with patent reproductive tracts. A positive duration trend was reported (p_{trend}=0.021). An age analysis, to estimate whether a woman was exposed to perineal talc prior to 1976 (when voluntary guidelines to prevent asbestos contamination of talcum powder were adopted) did not note differences between the age cohorts, suggesting that the composition of talcum powder did not alter the measure of effect.

In 2004, Mills et al. published a study of women from 22 counties in the Central Valley California region, diagnosed from January 1, 2000 through December 31, 2001, with cases identified through two population-based registries (40% response rate, n=256).[108] Controls were matched on county of residence identified through random digit dialing methods with a 57% participation rate (n=1,122). The questionnaire asked several questions about talc use, including: including adult use in the genital area, calendar year(s) of use, frequency of use (i.e., daily, several times a week) and total duration of use. Cumulative use was calculated by combining frequency (categorically weighted 0–3) and duration (in months) of use. 42.6% of cases and 37.1% of controls reported ever use of perineal talcum powder. Ever use of perineal talc was associated with ovarian cancer after adjustment (OR=1.37 (95% 1.02–1.85)). Trends examining frequency of use, duration of use, and cumulative use were all associated with increased risk (p-values$_{trend}$=0.015, 0.045, 0.05, respectively). Risk estimates were higher when restricted to invasive only (OR=1.51 (95% CI:1.07–2.12)) and women without tubal ligation (OR=1.54 (95% CI:1.10–2.16)).

In 2000, Ness et al. reported findings from a case-control study that recruited women ovarian cancer diagnosed from 39 hospitals around the Delaware Valley including contiguous counties in eastern Pennsylvania, Southern New Jersey, and Delaware.[108] There were 767 completed case interviews (88% of potentially eligible, incident cases). Controls aged 65 or younger were frequency matched by 5 year age group and ascertained by random digit dialing. 1,215 (74%) were interviewed. Women between the ages of 65 and 69 were identified through Health Care Financing Administration and frequency-matched to cases by county of residence and age group (n=1,367, 78% participation rate). The questions to assess perineal talc exposure were as follows: “As an adult and prior to [reference date] did you ever use talc, baby or deodorizing powder, at least once per month for 6 or more months on your: 1) feet, arms, or breasts, but not the genital or rectal areas? 2) genital or rectal area? 3) on your sanitary napkins? 4) on your underwear? 5) on your diaphragm or cervical cap?” They were then asked whether they had a male sexual partner(s) for more than a year who regularly used such products on his genital area or underwear. The duration of use of talc for each of these modes of exposure was also asked. Talc use on all areas of the body elevated ovarian cancer risk, even after adjustment for potentially important confounding factors. Similarly, talc use on sanitary napkins and underwear elevated ovarian

cancer risk (all OR for talc exposure ranged from 1.4 to 1.7) In contrast, talc use on diaphragms and/or cervical caps and use by the male partner did not appear to alter risk by much (OR=0.6 and 1.0, respectively). Years of use did not show a duration effect.

Table 5: Case-control studies examining the association between perineal talc use and risk of ovarian cancer

Study (year) [ref]	Overall measure of effect (95% CI)	Exposure (beyond ever/never)	Case/Control (#)	Dose-response?	Notes
Cramer 1982 [72]	1.92 (1.27, 2.90)	Years of diaphragm use	215/215	NA	Boston area
Hartge 1983[110]	0.70 (0.40, 1.1) (any mentioned) OR=2.5 (0.7, 10) (genital only)		197/197	NA	Washington DC (this was a brief report/letter)
Whittemore 1988[111]	1.45 (0.81, 2.60)	Years and applications per month	188/539	No	San Francisco, CA
Harlow 1989[45]	1.10 (0.70, 1.73)	After bathing ever/never	116/158 Tumors were borderline serous and mucinous	NA	Washington State. Deodorizing powders alone or in combination with other talc-containing powders had 2.8 times the risk (95% CI: 1.1-11.7) of women who had not had perineal exposure to powder
Harlow 1992[112]	1.50 (1.00, 2.25)	Years and frequency of use	235/239	Yes	Boston area, on a daily basis (OR 1.8, 95% CI 1.1-3.0), for more than 10 years (OR 1.6, 95% CI 1.0-2.7)
Rosenblatt 1992[113]	1.27 (0.97, 1.66)	After bathing/never Years of use, lifetime applications	812/1313	No	Washington State, borderline stronger association, low talc use
Tzonou 1993[114]	1.05 (0.28, 3.94)		189/200	NA	Very low use of talc (6 cases/7 controls)
Green 1997[115]	1.30 (1.10, 1.54)	Mention duration but not sure what measure	824/855	NA	Australia-Patent reproductive tract: with talc use (RR 1.3, 95% CI 1.0–1.7) compared to non-patent/no talc

Chang 1997[116]	1.42 (1.08, 1.86)	Duration (years) and frequency	450/564	Yes	Toronto duration of talc exposure and risk (OR 1.09, 95% CI 0.98–1.21, per 10 years of exposure)
Cook 1997[117]	1.60 (1.10, 2.33)	Duration and frequency measured not presented	313/422	NA	Western Washington State, invasive and borderline
Godard 1998[118]	2.49 (0.94, 6.60)		170/170	NA	French Canadian
Wong 1999[119]	1.00 (0.80, 1.25)	Duration (years)	499/755	No	Roswell Park hospital-based
Ness 2000[109]	1.50 (1.10, 2.05)	"At least once per month for 6 months or more"=ever	767/1367	No	Similar effect size for feet, perineal, underwear, sanitary napkin, no association diaphragm, duration in years
Mills 2004[108]	1.37 (1.02, 1.84)	Frequency, duration (years), cumulative use estimated	256/1122	Yes	Central California. Positive associations with freq, duration, cumulative exposure. No tubal ligation: OR= 1.54 (1.10–2.16)
Merritt 2008[107]	1.17 (1.01, 1.36)		1576/1509	Yes	Australian Patent tract only Positive duration
Gates 2008[106]	1.36 (1.14, 1.62)	Ever=at least once a week; duration and frequency data	1175/1202 210/600	Yes	Case-control New England and Nurses Health Study; evidence of dose-response
Moorman 2009[105]	1.06 (0.85, 1.32)		746/868 white 111/189 AA	NA	North Carolina-Large among of missing talc exposure data
Wu 2009[102]	1.53 (1.13, 2.09)	Ever/less than one year, years and frequency	LA-CA, same as 2015 609/688	Yes	Duration x frequency was also positive dose-response
Rosenblatt 2011[46]	1.27 (0.97, 1.66)	"after bathing" Ever/never	812/1313	No	Washington State, low talc use; Borderline: 1.55 (1.02, 2.37) no

					lifetime application trend
Kurta 2012[104]	1.40 (1.16, 1.69)	Ever/never	902/1802	NA	Fertility drug focus
Wu 2015[103] NHW Hispanic AA	 1.41 (1.21, 1.67) 1.77 (1.20, 2.62) 1.46 (1.27, 1.68)	Ever/less than one year	LA-CA 1265/1868 308/380 128/143	Yes	Trends seen for duration (every 5 years of use); PAR% presented
Schildkraut 2016[1]	1.44 (1.11, 1.87)		584/745	Yes	Non-serous: 2.28 (1.39, 3.74); noted dose response with both duration and lifetime applications. Association with nongenital also
Cramer 2016[74]	1.32 (1.15, 1.51)		2041/2100	Yes	Freq/duration dose response noted

Exposure is perineal unless otherwise noted.

The case-control studies that have accumulated over the last 5 decades are strong evidence that there is an association between perineal talc use and ovarian cancer. Of the 23 studies presented in Table 5, 19 of 23, or 82.6%, indicate a positive association. The majority (12 of 19) of the positive associations were statistically significant at a 95% confidence level. A single, small study showed lower risk (it should be noted talc use was whole body, not defined as perineal) and a second study was null.[109,118] Two others had very low talc use or a large amount of missing talc exposure data.[105,114]

There were 14 case-control studies that were designed to assess dose-response. Nine (64.2%) supported a dose-response effect, either in duration (number of years using), frequency, or a combined frequency and duration variable to calculate dose.[1,74,102,103,106–108,112,116]Five did not note a dose-response relationship (35.7%).[46,109,111,113,119]

XII. Talc as a Causal Factor in Ovarian Carcinogenesis

This review focused on primary epidemiologic literature, meta and pooled analyses, the systematic reviews, commentaries and other statements that examined talc use and risk of ovarian cancer. I also examined original literature regarding the biological mechanisms that might drive this association, including research in humans, animal models, and cell lines. I reviewed the chemical properties of talc, with the assumption that the talcum powder was free of asbestos. I considered what the multiple lines of evidence meant individually and in totality, as I formulated my opinion. I returned to the guidelines described by Sir Austin Bradford Hill as the best way to describe how I reached my conclusion.

In 1965, Dr. Hill, at the time a Professor Emeritus of Medical Statistics, at the University of London published the seminal manuscript, “The Environment and Disease: Association or Causation?” in the *Proceedings of the Royal Society of Medicine*.[120] In it, he described his viewpoints on 9 areas to consider when assessing whether the relationship between an environmental factor and an outcome could be deemed causal. Here, I describe my interpretation of his viewpoints, considering updates to what has been discovered about human health and disease over the last five decades since, “Hill’s Criteria”, as they have become colloquially known, were published. The quotes below are taken from this publication unless otherwise referenced.

Strength and Consistency

Hill noted that the first two considerations, strength of association and consistency, could be considered together. The first factor presented was strength of association—the measure of effect between the exposure and disease. In epidemiologic studies, this is generally the relative risk or odds ratio, with larger effect sizes considered to be stronger evidence of a causal association. However, Hill notes that, "We must not be too ready to dismiss a cause and effect hypothesis merely on the grounds that the observed association appears to be slight." More modest measures of effect may be due to rareness of the outcome or an uncommon exposure. The second factor, consistency, is the assessment of other studies, carried out in different populations. One cannot assess consistency for a single study, but several studies with similar measures of effect would be evidence that there is a consistent association between the exposure and disease.

The effect sizes seen in most of the studies examining the association between the genital use of talcum powder and ovarian cancer are around 1.25 in magnitude, but that does not make them untrue or unimportant. The risk estimates in most individual case-control studies and the summary risk estimates from the meta-analyses are of a magnitude (~1.25) that is comparable to other common exposures that are causally related to cancer (e.g., combined and progestogen-only hormonal contraceptives and breast cancer risk, alcohol use and colorectal cancer).[121,122] The 3 cohort studies found lower effect sizes, which may reflect the smaller number of cases in these studies or the failure to correctly or completely classify use of talc. Both WHI and NHS reported positive associations between perineal talc use and ovarian cancer. Misclassification of talc use in the Sister Study findings coupled with the small number of cases limited the utility of the original report, now updated with an additional n=138 ovarian cancer cases. The detailed assessment of misclassification and recall bias in the updated Sister Study cohort now supports a positive association between perineal talc use and ovarian cancer, after a stringent analysis controlling for bias and missing data. Thus, both case-control and cohort studies report overwhelmingly consistent findings.

In my opinion, having reviewed hundreds of epidemiologic studies and publishing my own pooled and meta-analyses, the consistency of the effect sizes seen across populations is strikingly consistent. The simple ever/never measure of perineal talc and the association with ovarian cancer was nearly constant regardless of study population, decade of study enrollment, and race and ethnicity. This effect is not diminished whatsoever by the strength of the association. Taken together I give strong weight to the strength of association and consistency reported in over 3 dozen studies in multiple populations.

Specificity

The third factor described by Hill was specificity between the exposure and outcome, meaning the exposure only caused one disease. While including this as a point of consideration, Hill also noted that this would be a very strong piece of evidence if it were the case, but that it was likely a particular exposure could cause many different diseases. He noted the case of cigarette smoking (his area of expertise) with both lung and nose cancers, and also gave the example of milk being a vector for various infectious agents that caused a host of diseases. Thus, specificity has generally not been strongly considered when examining causality.

I concur with Hill that specificity plays less of a role today as most diseases are multifactorial; however, the reports regarding perineal talcum powder and endometrial cancer are intriguing and offer some evidence that the talc-ovarian cancer association may be specific, as the handful of studies examining talc-endometrial cancer report no associations (reviewed in Wentzensen & O'Brien).[88] Additional evidence by O'Brien et al. examining risk of both breast and uterine cancers with genital talc exposure in the Sister Study and finding a null association adds more weight to this factor, as they note a talc-ovarian cancer association in this population with the addition of cases identified since the initial analysis was published.[95] Overall, I think the literature provides support for specificity, I would give this factor a moderate weight.

Temporality

Temporality was described as the fourth factor, a simple concept as to whether the exposure occurred before the disease. While conceptually simple, it can be more difficult to determine in diseases where there is a long latency period between the exposure and the onset of clinically apparent disease. Similarly, the idea that there may be windows of susceptibility where exposures during that time period are particularly deleterious, can make temporality difficult to ascertain. Regardless, this is an important consideration when assessing causality, because if the exposure clearly did not occur before the disease, there would be no causal association. In the case of perineal talc exposure, both case-control and cohort studies establish a temporal association between perineal talc and ovarian cancer. A good example of this is from the Sister Study, which originally reported that 14% of women had used perineal talc in the last year. When they went back again and asked from ages 10-13, an additional 14% reported use.[76] In addition, use on feminine hygiene products and diaphragms (reported in several studies) suggests usage during premenopausal, child-bearing years, and ovarian cancer is generally a disease of later onset—thus temporality is highly likely. I would consider this a factor of moderate weight.

Biologic gradient

The fifth factor described was the idea that a biological gradient, or a dose-response association is present, with increased exposures (either in time or intensity) leading to a greater risk of disease. As with temporality, it is simple in concept but can be difficult to assess in real life. A dose-response relationship assumes a linear association between the exposure and disease and does not consider that there may be a low threshold of exposure that is sufficient to cause disease (i.e., after a certain intensity or duration, risk does not increase). Additionally, the biological gradient does not take into account windows of susceptibility; however, if present, it can provide good evidence supporting causality (see pack years of cigarette smoking and risk of tobacco-related cancers).

The majority of studies that collected data on frequency and duration were case-control studies and showed evidence of a dose-response relationship (64.2%, reviewed in section XI). Five of the 14 did not, but this is to be expected given the multiple ways exposure was measured across studies. Perineal talc exposure is difficult to measure. While number of applications and years of is a straightforward way to assess dose (i.e., frequency of use multiplied by years of use), the amount of perineal talc used is not quantified. It is likely the amount of talc that can travel up into the reproductive tract that is most important, and that measurement would not be possible to determine in epidemiologic studies. For this particular exposure-disease association assessment, I would weigh biologic gradient as having moderate weight.

Biological plausibility

Biological plausibility was described as the sixth factor with the caveat, "…But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day." Often, biologically plausibility is supplemented by studies in other model systems (rodent models, cell lines) with the idea that this extends to humans. Lack of biological plausibility may simply be a limitation of scientific knowledge.

I found sufficient support that it was biologically plausible that talcum powder applied to the genital area can reach the fallopian tubes and ovaries. Studies have demonstrated that talc has been found in ovarian tumors and other tissues in the reproductive tract, likely through migration of talcum powder from the perineal region through the genital tract. Human studies were more convincing than animal studies, likely due to the difficulties in replicating what is often a lifetime of use of talc in humans to dosing and administration in animals (whose physiology may not closely align with human female genital tract). The observation that larger measures of effect are seen among women with a patent reproductive tract who use perineal talcum powder provides additional support regarding the biological plausibility of the association.[87] Once present in the fallopian tubes and/or ovaries, components of talcum powder, including those known to be Group 1 carcinogens (asbestos, fibrous talc, heavy metals), can induce an inflammatory response. It is well-accepted that inflammation contributes to the initiation,

development, and progression of cancer, including ovarian cancer.

I weighted biological plausibility as a strong factor.

Coherence

The seventh factor, coherence, advises that the relationship between the exposure and disease should not be far afield from what is generally understood about the underlying biology of the disease. Similar to biologic plausibility, this may be limited by scientific knowledge. Overall, the proposed biologic mechanisms of ovarian carcinogenesis due to talc exposure fit with what is currently known about the etiology and natural history of ovarian cancer, and with other cancers. Specifically, the association between inflammation and cancer was postulated by Virchow in 1863 and has been studied by thousands of investigators across the globe.[123] As stated in the review by Coussens and Werb, "Many cancers arise from sites of infection, chronic irritation and inflammation. It is now becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration."[123] Aside from the cell line work by Fletcher et al. and Mandarino et al., this is also supported by research in endometriosis, an inflammatory benign gynecologic condition, as an established risk factor for ovarian cancer.[21,64,66] I weighted coherence as a moderate factor.

Experimental evidence

The eighth factor is experimental evidence. It would be unethical to intentionally expose women to talc, given what observational studies have shown thus far, hence these data are not feasible. As examining talc exposure and ovarian cancer in humans is feasible only through observational studies, experimental evidence could be gathered if the exposure was discontinued (e.g., women quit using perineal talc) and the risk of ovarian cancer decreased—but this would take decades. This factor is not considered in the overall analysis to determine causality between perineal talc and ovarian cancer.

Analogy

With respect to analogy, if there was an established causal relationship between a similar exposure and disease, it would add support to this line of evidence. In other words, the relationship is in line with other similar exposure-disease associations. An example of this would be the established cigarette— lung cancer association, and the cigar—lung cancer association. While both are combustible tobacco products, there are some differences in patterns of use, amounts and types of chemicals, etc.; however, both are tobacco-based, similar exposures. Here, as with coherence, the relationship between inflammation and various cancers has been well-established. As "cancer" is a group of complex diseases, there are many possible analogies, thus I would weight this as a low factor in assessment of causality.

It should be noted that Hill himself stated that these 9 factors should not be considered "hard and fast" rules of evidence that must be met before a causal determination was made. Instead, they should be considered as a whole, and help answer the question, "is there any other answer equally, or more, likely than cause and effect?"

XIII. Summary Opinion

Johnson & Johnson talcum powder is a common product that has been used by generations of women for personal care. Ovarian cancer is a relatively rare cancer, but the morbidity and mortality caused by this disease is severe. As a rare disease, and one with a long latency period, case-control studies are the most common type of epidemiologic study used to identify risk factors for ovarian cancer. Given the prevalence of perineal talc use among women in the population (not a rare exposure in most populations), case-control studies are appropriate to assess the hypothesis that genital talc use is associated with ovarian cancer. Cohort studies are also appropriate and have the advantage of better defining the temporal association between the exposure and the disease; however, current studies lack the detail of some case-control studies with respect to duration or intensity of exposure and need additional follow up time. The meta and pooled analyses, while utilizing data from the cohort and case-control studies, allow for additional analyses and provide the ability to examine subgroups. I considered the strengths and weaknesses of each design and the rigor of each individual study when providing a comprehensive evaluation of these data. I also considered multiple lines of evidence, including findings from pathology, cancer biology, and toxicology when making a determination about whether the potential mechanism(s) driving the association between perineal talc use and ovarian cancer are scientifically sound.

I considered the totality of the evidence through the lens of Dr. Hill's factors and highlight below the points that support my opinion that the association between perineal talc use and ovarian cancer is causal.

- Talcum powder and its components (platy talc, asbestiform talc, asbestos, heavy metals, and other chemicals) can migrate from the perineum to the ovary and/or other pelvic tissues, causing an inflammatory environment in some women.

- Inflammation creates a cascade of reactions that ultimately promote carcinogenesis.

- There is a strikingly consistent association between ever use of perineal talc and ovarian cancer that has persisted across studies with participants from over 5 decades, and from across the world.

- The estimates from individual studies and the summary estimates from the meta-analyses are of a magnitude (~1.25) that is comparable to other common exposures that are causally related to cancer.

- The biases that could potentially result in an over or under estimate of the measures of effect did not invalidate the associations seen between use of perineal talc and ovarian cancer risk. A detailed assessment of recall bias and misclassification bias, using cohort data from the Sister Study, provide additional support that the association is not being driven just by these biases.[95]

- That despite the difficulties in measuring exposure to perineal talc, a dose-response relationship was often identified.

For these reasons, based on my education, training, and experience and the totality of evidence, it is my opinion to a reasonable degree of scientific certainty that the genital use of Johnson's Baby Powder and Shower to Shower can cause epithelial ovarian cancer. I reserve the right to revise my report if additional information is made available. I also reserve the opportunity to review and comment on the expert reports and testimony submitted by Defendants.

Michele L. Cote, PhD, MPH

November 15, 2023,

updated May 28, 2024

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Appendix A: Curriculum Vitae

MICHELE LYNN COTE

Work Address: 550 University Blvd AOC 6047 Indianapolis, IN 46202
Telephone: (317) 274-6460
Work email: mlcote@iu.edu
Personal email: Michele.Cote@gmail.com
Date prepared: November 7, 2023

PROFILE

Dr. Cote has over 20 years of experience in scientific research, scientific review, and educational program management. As an internationally recognized molecular cancer epidemiologist with a focus on the intersection of health disparities and cancer incidence and prognosis, she rose through the academic and administrative ranks at Wayne State University in Detroit, Michigan. In her role as Associate Center Director for Cancer Research Training and Education at the Karmanos Cancer Institute, a NCI-designated comprehensive cancer center, she focused on trainee development across the spectrum, from high school through tenured basic science and clinical faculty. As the Vice Chair for Diversity, Equity and Inclusion for the Departments of Oncology and Otolaryngology, she worked closely with faculty, chairs, deans, and the Office of the Vice President for Research to actively and continuously support an equitable academic environment. Finally, as leader of the Environment and Cancer Research Interest Group leader for the NIEHS-supported Center for Urban Responses to Environmental Stressors, she focused on assembling multidisciplinary teams to develop new collaborative projects. These projects had the dual goal of increasing extramural funding while ensuring the work is impactful and important to community members in Detroit and the surrounding metropolitan area. She is an innovative, versatile, collaborative research scientist, with leadership, financial, and strategic planning experience across academia and non-profit organizations. She joined Indiana University and the Simon Comprehensive Cancer Center in September 2022 as the Director of the Susan G. Komen Tissue Bank and a Professor in the Fairbanks School of Public Health.

EDUCATION

	DATES
Graduate:	
Ph.D.—Epidemiologic Sciences--University of Michigan, Ann Arbor, MI	2000-2004
M.P.H.—Epidemiology--University of Alabama, Birmingham, AL	1995-1996
Baccalaureate:	
B.S.--Biology--University of Michigan, Ann Arbor, MI	1990-1994

FACULTY APPOINTMENTS

Indiana University Fairbanks School of Public Health, Department of Epidemiology, Professor (with tenure)	9/2022-
Director, Susan G. Komen Tissue Bank at Indiana University	9/2022-

Carrie Glasscock-West Endowed Chair of Breast Carcinogenesis	9/2022-
Wayne State University School of Medicine, Departments of Oncology and Otolaryngology, Vice Chair for Diversity, Equity and Inclusion	5/2021-8/2022
Wayne State University School of Medicine, Department of Oncology, Professor (with tenure)	8/2019-8/2022
Associate Center Director for Cancer Research Training and Education, Karmanos Cancer Institute	1/2016-8/2022
Wayne State University School of Medicine, Department of Oncology, Associate Professor (with tenure)	8/2011-7/2019
Wayne State University School of Medicine, Department of Oncology, Assistant Professor	7/2010-7/2011
Wayne State University School of Medicine, Department of Internal Medicine, Assistant Professor	1/2005-6/2010
Wayne State University School of Medicine, Department of Family Medicine, and Public Health Practice Graduate Faculty	1/2006-8/2022
Karmanos Cancer Institute Population Studies and Disparities Research Program, Member	1/2005-8/2022

MAJOR PROFESSIONAL SOCIETIES

International Association for the Study of Lung Cancer	2010-2013
American College of Chest Physicians	2006-2013
Society of Epidemiologic Research	2005-2010
American Association of Cancer Research	2000-present
Molecular Epidemiology Working Group*	
Molecular Epidemiology Working Group Steering Committee	2020-2023
*As of 2022, the Population Sciences Working Group	
International Genetic Epidemiology Society	2000-2010

HONORS/AWARDS

John Snow Award, Epidemiology Section, American Association of Public Health	2020

Outstanding Graduate Mentor Award in Health Sciences, Wayne State University	2018
Dr. Michael J. Brennan Scientific Distinction Award, Heroes of Breast Cancer	2015
College Teaching Award, Wayne State University School of Medicine	2011

SERVICE

Wayne State University

Departmental/Divisional

Karmanos Cancer Institute Biobank Oversight Committee	2018-2022
Cancer Biology Student Day, Judge	2015-2022
Steering Committee Member, Cancer Biology	2015-2022
Search Committee Member: Molecular Imaging & Diagnostics Program	2013, 2021
Search Committee Member: Population Sciences	2010, 2014-15, 2021-2022
Coordinator: Population Studies and Disparities Monthly Meetings	2009-2010, 2014-2018
Coordinator: Population Studies and Prevention Annual Retreat	2009, 2015
Member, Sleep Medicine Training Grant Working Group	2007-2008
Co-Chair, Lung Cancer Working Group	2007-2015

School of Medicine

Faculty Development Liaison, Oncology	2020-2022
Poster/Presentation Judge, Lifespan Alliance Research Day	2019
Recruiting/Poster Judging ABRCMS National meeting	2014, 2016
MD/PhD Candidate Interviews	2016-2022
IBS Recruitment/Admission Committee Member: Cancer Biology	2010-2011, 2014-2017
Admissions Committee Member: MPH Program	2010-2011, 2014-2015

University

Search Committee Member: Environmental Health Sciences	2018, 2021-2022
Search Committee Ad Hoc Member: Undergraduate Public Health	2020
Co-Chair, Arab American Community Economic and Social Services & Wayne State University Research Enhancement Initiative	2019-2022
Graduate Student Research Day Poster Judge	2016, 2017, 2018
Invited Panelist, Professional and Academic Development Seminar, "NIH and NSF Career Award Advice from WSU Recipients and Reviewers"	2011
Chair, WSU President's Commission on the Status of Women	2007-2008
Vice-Chair, WSU President's Commission on the Status of Women	2006-2007
Member (Former Chair), Health Sciences Committee, WSU President's Commission on the Status of Women	2005-2009
Commissioner, WSU President's Commission on the Status of Women	2005-2009

Community

Interview, iHeart Radio, Sista Strut for Breast Cancer	2018
Komen for the Cure, Greater Detroit, Invited Scientific Speaker	2017, 2018
Interview, Black American Journal: Breast Health	2017
Principal Investigator and Host, Komen Normal Tissue Bank Collection	2016
Komen for the Cure, Greater Detroit, Board Member, Executive Committee	2016-2020
Street Beat, Invited Guest: Komen Race for the Cure	5/9/2015
LungForce/American Lung Association Region B, Board Member	2015-2017
LungForce, Invited Speaker, Belle Isle	2014
Health Talk, Bloomfield Michigan Public Television, Invited Guest	2014
On The Floor, Breast Cancer Awareness, The Impact Network, Invited Guest	2014

Metropolitan Detroit LUNGevity Walk, Invited Speaker	2008, 2009
Hurricane Katrina Family Identification Team, Baton Rouge, LA	2006
Ford Motor Company, Invited Speaker	2005

Scholarly Service

Grant Review Committees

National/International

Reviewer, End Breast Cancer NOW Foundation, UK	2023
Reviewer, National Cancer Institute, SEP-10: Ovarian and GYN	2022
Reviewer, National Institute for Health Research, UK	2022
Reviewer, Conquer Cancer: The ASCO Foundation Career Development and Young Investigator Awards	2021
Site Visitor, NCI Integrative Tumor Epidemiology Branch	2021
Reviewer, World Cancer Research Fund International	2021
Reviewer, National Cancer Institute, CCSG: ZCA1 RTRB-0 (O1)	2021 (2 panels)
Reviewer, The Netherlands Organisation for Scientific Research (NWO/ZonMw)	2021
Reviewer, National Cancer Institute, CLAS-B (March, June)	2020
Reviewer, National Cancer Institute, "P20-Feasibility and Planning Studies for SPOREs to Investigate Cancer Health Disparities" (ZCA1 RPRB-L (J1))	2019
Chair, National Cancer Institute, Special Emphasis Panel: "Mechanisms of Disparities in Etiology and Outcomes of Lung Cancer"	2019
Site Visitor, NCI Metabolic Epidemiology Branch	2018
Paper & Publications Review Committee (includes grants), Women's Health Initiative	2018-present
Reviewer, National Cancer Institute (NCI-J) K-series Mentored Research Awards	2018, 2020, 2021

Reviewer, French National Cancer Institute (INCa), "Research in Human and social sciences, epidemiology and public health"	2017, 2019, 2020
Reviewer, National Cancer Institute, Planning Grants for Global Research Infrastructure in Non-Communicable Disease	2016
Reviewer, Komen Career Catalyst Research Grants	2015
Reviewer, Komen Career Catalyst Research Grant Committee—Letter of Intent pre-review	2014, 2016
Reviewer, ad hoc, National Institute on Minority Health and Health Disparities P20 Pilot Studies Limited Competition Grants	2014
Reviewer, ad hoc, National Cancer Institute Specialized Program of Research Excellence (SPORE)	2014
Reviewer, ad hoc, National Cancer Institute Cancer Etiology Study Section	2012
Reviewer, ad hoc, National Cancer Institute "Provocative Questions"	2012
Reviewer, ad hoc, National Institute on Minority Health and Health Disparities P20 Exploratory Health Disparities Centers of Excellence	2011
Reviewer, ad hoc, National Cancer Institute P20 Feasibility Studies for Collaborative Interaction for Minority Institution/Cancer Center Partnership	2011, 2015, 2017
Reviewer, ad hoc, National Center on Minority Health and Health Disparities Loan Repayment Program Applications	2010, 2012, 2013, 2014, 2015 (2 panels)
Reviewer, ad hoc, National Cancer Institute Special Emphasis Panel, NCI-ARRA Grand Opportunity	2009
Reviewer, ad hoc, National Cancer Institute, PAR 06-294, Small Grants Program for Cancer Epidemiology (now R03/R21 omnibus)	2008 (2 panels), 2009 (2 panels), 2010, 2011(2 panels), 2012 (2 panels), 2013, 2014 (2 panels),
Mail Reviewer, National Lung Cancer Partnership Career Development Award	2007, 2008, 2010

Reviewer, ad hoc, National Heart, Lung and Blood Institute	2006

Regional/Local

Reviewer, American Cancer Society/KCI Block Research Grants	2017, 2018
Reviewer, Henry Ford Health System Career Development Grants	2015
Reviewer, University of Cincinnati Environmental Health Center Grant Pilot Projects	2015-2021
Judge, Henry Ford Health System Annual Research Symposium	2010
Reviewer, Kentucky Lung Cancer Research Program	2009, 2015
Reviewer, Pre and Post-doctoral Fellowships in Cancer Prevention, University of Texas, M.D Anderson Cancer Center	2007
Reviewer, Del Harder Research Award, Rehab Institute of Michigan, Detroit Medical Center	2007, 2008

Service for Peer-Reviewed Journals

Review Editor	
Editorial Board—Cancer Research	2016-2021
Statistical Editor-Journal of the National Cancer Institute (JNCI)	2013-2020
Frontiers in Applied Genetic Epidemiology	2010-2012

Review of Manuscripts
American Journal of Epidemiology, Breast Cancer Treatment & Prevention, BMC Cancer, Cancer, Cancer Biomarkers, Cancer Epidemiology Biomarkers and Prevention, Cancer Research, Carcinogenesis, Clinical Cancer Research, Disease Markers, Endocrine Related Cancers, Gynecologic Oncology, Human Genetics and Genomics Advances, Journal of Clinical Oncology, Journal of the National Cancer Institute, Journal of Thoracic Oncology, Journal of Women's Health, Lancet Oncology, Molecular Carcinogenesis, PLOS ONE, Respiration, Respiratory Medicine

Other Scholarly Service

AACR Abstract Reviewer	2022
AACR Cancer Epidemiology and Prevention Award Committee	2020-2022
American Society of Preventive Oncology, Annual Meeting Planning Committee & Panel Chair	2020

Member, Steering Committee, AACR Molecular Epidemiology Group* *now known as the Population Sciences Working Group	2020-present
Arab Health Summit National Steering Committee	2018-present
State of Michigan BioTrust Scientific Advisory Board	2018-present
Epidemiology of Endometrial Cancer Consortium, Steering Committee	2016-present
Epidemiology of Endometrial Cancer Consortium, Member	2010-present
Centers for Disease Control and Prevention. The Intersection of Public Health Genomics, Academia and Government. Invited participant to this two day working meeting, Ann Arbor, MI	2008
Michigan Department of Community Health. Newborn Screening Dried Blood Spots BioBank: Implications for Research and Public Health. Invited participant to this single day working meeting. Ann Arbor, MI	2006
International Lung Cancer Consortium, Familial Risk committee	2006-2010
Michigan Cancer Genetics Alliance, Research Committee	2005-2015

TEACHING
Wayne State University
Classroom/Didactic

Guest lecture: Environmental health (FPH 7420), "Gene X Environment Interactions and Cancer" 75 minute lecture.	2017, 2018, 2019, 2020, 2021, 2022
Co-Instructor: Special Topics in Cancer Biology, "Emerging Issues in Breast Cancer Disparities Research" (1 credit). This 8 week summer course is required for all Komen trainees. Co-led by Dr. Kristen Purrington.	2016
Co-Instructor: Family Medicine and Public Health Practice: Introduction to Epidemiology (FPH 7240-3 credits). This 14 week course is required for all MPH students. It is offered annually Fall semester and is attended by a mix of graduate and medical students. I set the learning objectives, organized the syllabus, coordinated guest lecturers, created exams and assigned grades.	2015

Guest lecture: Cancer Epidemiology (CB 7430), "Tobacco and Cancer" 75 minute lecture	2019, 2016, 2015, 2013, 2011
Guest lecture: Cancer Epidemiology (CB 7430), "Biomarkers and Cancer" 75 minute lecture	2013
Guest lecture: Introduction to Cancer Biology (CB 7250), "Cancer Epidemiology" 60 minute lecture	2007, 2008, 2010, 2011, 2012
Guest lecture: Applied Epidemiology (FPH 7250)	2013
Guest lecture: Center for Molecular Medicine and Genetics (Genetic Counseling). "Developing a Research Project" 90 minute annual lecture	2008-2012
Co-Instructor: Family Medicine and Public Health Practice: Applied Epidemiology (FPH 7250). This 14 week course is required for MPH students with a concentration in Public Health Practice. Held annually Winter semester and attended by a mix of graduate and medical students. I set the learning objectives, organized the syllabus, coordinated guest lecturers, created exams, and assigned grades.	2007-2011

Residents/Fellows

Guest lecture: Gyn Onc Educational Seminar. "Cancer Epidemiology" 60 minute guest lecture as part of a seminar series	2012
Guest lecture: Pathology Department Seminar. "Epidemiology in Medicine" 90 minute lecture	2008

Faculty

Member, Sleep Medicine Collaborative Training Grant. "Complex disorders: identifying germline mutations via epidemiological studies." 60 minute lecture	2008

Teaching at other institutions-University of Michigan, Ann Arbor

Graduate Students

Guest Lecture: University of Michigan School of Public Health, Cancer Epidemiology Course, "Epidemiology of Endometrial Cancer", 75 minute lecture	2013-2022
Guest Lecture: University of Michigan School of Public Health, Cancer Epidemiology Course, "Cancer Registries and Surveillance", 60 minute lecture	2013-2022

Guest Lecture: University of Michigan School of Public Health, Genes and the Environment Course, "Lung cancer and the environment", 60 minute lecture	2012, 2017
Guest Lecture: University of Michigan School of Public Health, Chronic Disease Epidemiology Course, "Cancer Registries and Surveillance", 60 minute lecture	2010
Guest Lecture: University of Michigan School of Public Health, Topics in Cancer Prevention Course, "Lung Cancer", 60 minute lecture	2010

Mentorship

MPH Mentor, Kristen Cunningham, Indiana University Fairbanks School of Public Health	2023-
Dissertation Committee Member, Afrin Sultana Chowdhury, Pharmacology and Toxicology, Indiana University School of Medicine	2023-
Dissertation Committee Member, Teresa Imburgia, Department of Epidemiology, Indiana University Fairbanks School of Public Health	2023
Dissertation Committee Member: Katherine Ridley-Merriweather, Health Communication, Indiana University Purdue University, Indianapolis	2023
Research Advisor, Rosa Polin, MD, Gynecologic Oncology Fellow Wayne State University	2021-2022
Research Advisor, Larissa Mattai, MD, Gyencologic Oncology Fellow Wayne State University	2021-2022
Dissertation Committee Member and Deans Diversity Advisor, Gabriel Mpilla, Current: Lab manager, Stankovi Lab, Stanford University	2018-2021
Komen Trainee and Deans Diversity Advisor, Morenci Manning-Powell "Clinical Significance, functional role and molecular mechanism of 2'-O-Methyltransferase Ftsj3 in promoting cancer progression" Currently: Medical Science Liaison, Johnson & Johnson	2018-2021
External Advisory Committee, Justin Colacino, PhD, University of Michigan, as part of his NIEHS ONES Award: "Developmental Exposures, Stem Cell Reprogramming, and Breast Cancer Disparities".	2017-2000
Dissertation Co-Chair, Megan Mullins, PhD Candidate, University of Michigan School of Public Health Department of Epidemiology, Dissertation:	2016-2020

"Understanding end-of-life care among women with ovarian carcinoma: racial differences in clinical practice and policy response."
Currently: Assistant Professor (tenure track), University of Texas Southwestern

Dissertation Chair, Andreana Holowatyj, Dissertation: *"Clinicopathology and molecular determinants underlying benign breast and breast cancer lesions."* 2015-2017
Currently: Assistant Professor (tenure track), Vanderbilt University, Epidemiology

Dissertation Chair, Asra Shaik, MD/PhD student, Cancer Biology, Dissertation: *"Characterizing novel radiologic and pathologic tissue-based risk factors for breast cancer in African American women with benign breast disease."* 2015-2018
Currently: 1st year Fellow, Hem/Onc, The University of Washington/Fred Huc

Research Advisor, Hyo Park, MD, Gynecologic Oncologist 2015-2019
Currently: Gynecologic Oncology Associates, Los Angeles, CA

Rotation mentor and Committee Member, Kayla Connor, PhD Candidate, 3rd year Cancer Biology, Dissertation: *"Role of the APOBEC3 family of Cytidine Deaminases in mediating Cisplatin and Carboplatin response."* 2015-2020
Currently: Scientist III, Bioinformatics, Thermo Scientific

Advisor, J1-International Scholar: Pratthana Yongsakulchai, Khon Kaen University, Thailand, "SNPs associated with coronary artery disease in a Thai population." 2013
Currently: Assistant Professor, Thammasat University, Thailand

Summer research advisor: Susanna Mitro, University of Michigan MPH 2014, "Clinical characteristics of breast cancers in African-American women with benign breast disease: A comparison to the Surveillance, Epidemiology and End Results Program." 2013
Currently: Research Scientist, Kaiser Permanente, Division of Research

Cancer Biology Independent Study Student: Brittany Haynes 2013
Currently: Scientific Program Specialist · National Center for Advancing Translational Sciences

Dissertation committee member: Shama Virani, University of Michigan PhD 2014, "Effect of Environmental Exposures on Cancer May Be Mediated Via Epigenetic Mechanisms." 2012-2014
Currently: Scientist, International Agency for Research in Cancer (IARC), Lyon, France

Master's Thesis Advisor: Michael "Jay" Harrison, Genetic Counseling Graduate, Wayne State University. Thesis: Re-contact of lung cancer study 2010-2011

subjects to consent allowing dbGap access to de-identified GWAS data.
Currently: Owner, Peared Creation

Family Medicine and Public Health Practice Independent Study (3 credits). 2010-2010
Student: David Edwards, PharmD. Topic: Oncogene mutations in lung cancers. This independent study resulted in a peer-reviewed publication.
Currently: Associate Dean, Faculty of Science, University of Waterloo

Dissertation committee member: Alison Van Dyke, MD, PhD 2007-2009
PhD 2009, "Inflammation in non-small cell lung cancer: associations with risk and survival in women"
Currently: Pathologist and Direct of the SEER-linked Virtual Tissue Repository, National Cancer Institute, Surveillance Research Branch

Master's Thesis Advisor: Shawnita Sealy-Jefferson, MPH (5/2008), Wayne State University. Thesis: Racial differences in prevalence and risk factors associated with osteoarthritis and rheumatoid arthritis in Caucasian and African American women. 2007-2008
Currently: Associate Professor with tenure, The Ohio State University

Master's Thesis Advisor: Julie J. Ruterbusch, MPH (5/2007), Wayne State University. Thesis: Increased risk of secondary kidney tumors: a population-based analysis. 2006-2007
Currently: Director, Epidemiology Core, WSU and Karmanos Cancer Insitute

Master's Thesis Advisor: Jessica Naff, MPH (5/2007), University of Michigan. Thesis: Racial differences in cancer risk among relatives of early-onset lung cancer cases. 2006-2007
Currently: Pediatrician, Navy Medicine Support Command, Jacksonville, Florida

Course or curriculum development
MPH Curriculum Committee—Epidemiology tract 2012
Accreditation Committee Genetic Counseling Program, Internal Review (Committee Chair, Research Plan) 2012

Wayne State University Master of Public Health, Epidemiology Concentration 2011-2014

Wayne State University Master of Public Health, SAS course 2010-2011

MPH Project Task Force (subcommittee of the Curriculum committee) 2007

Accreditation Committee Genetic Counseling Program (Internal Review) 2007

GRANTS, CONTRACTS, AND OTHER FUNDING

Active National/International Grants and Contracts

OGKTB1301(PI: Cote)
The Susan G. Komen Tissue Bank at the IU Simon Comprehensive Cancer Center
$1,250,000 (total); 10% effort
1/1/2023-6/30/2025
This is a novel biorepository with longitudinal data that collects, stores and annotates healthy breast tissue from volunteers. These specimens are provided to researchers both internally and worldwide.

OGKTB2201 (PI: Cote)
Biorepository Partner
$645,242 (total); 1% effort
4/1/2022-3/31/2024
The Komen Tissue Bank will additionally serve as the biorepository for a large-scale national breast cancer project.

5R01CA237607-04 (PI: Degnim)
$35,795 subcontract; 5% effort (Co-I: Cote)
9/1/2020-5/31/2025
Biomarkers to improve targeting of breast cancer prevention in women with atypical hyperplasia
We will provide a validation set of benign breast biopsies of African-American women with and without a subsequent breast cancer.

Released due to move to Indiana University

1T32GM139807 (MPI: Chow, Cote, Lanier (contact))
"Initiative for Maximizing Student Development"
2/1/2021-1/31/2026
$471,620 (year 1 direct); 5% effort
Building off five decades of successful recruitment and retention of underrepresented students in STEM fields, this new funding mechanism will focus on training 10 doctoral students in the biomedical sciences.

NCI 2P30 CA022453-34 (PI: Bepler)
Cancer Center Support Grant
$1,900,000; 10% effort
08/08/1997-9/11/30/2025
Role: Associate Center Director for Cancer Research Training & Education Coordination
The Karmanos Cancer Institute is a NCI-designated Comprehensive Cancer Center. Dr. Cote facilitates education and career development across the institution. Dr. Cote also has supplemental support to increase tobacco cessation services at Karmanos Cancer Institute.

R01CA237318-01A1 (PI: Schildkraut)
$55,412; 5% effort (Site PI: Cote)

7/1/2020-6/30/2025
Ovarian Cancer Survival in African-American Women
This study will gather survivorship information on a large number of African-American ovarian cancer cases and controls that will allow us to make meaningful assessments of factors related to outcomes for African Americans.

5R01CA237602 (PI: Radisky)
$35,795 subcontract; 5% effort (Co-I: Cote)
9/1/2020-5/31/2025
Involution-based biomarkers of breast cancer risk
This study utilizes multiple technologies to assess involution in benign breast biopsies of African-American women with and without a subsequent breast cancer.

NCI R13CA250188-01 (MPI: Cote, Du)
$25,000 (total)
No effort
Approaches to Curtail Endometrial Cancer Incidence and Mortality
This conference grant was awarded to bring together endometrial cancer researchers from across the globe to highlight the current progress and challenges in endometrial cancer control. The award has been extended until April 2023.

Active Other Grants and Contracts

Previously funded Grants and Contracts

NCI 1R01CA200864-01A1 (PI: Cote)
5/1/2016-4/30/2023 (NCE)
"Molecular Classification of High Grade Endometrial Cancers: Extending TCGA Findings to a Diverse Population"
$ 1,855,068 (total direct); 25% effort

NCI R13CA250188-01 (MPI: Cote, Du)
$25,000 (total) No effort
Approaches to Curtail Endometrial Cancer Incidence and Mortality

Michigan Department of Health and Human Services (PI: Cote)
11/01/2015 – 09/30/2022
"Lung Cancer Screening and Tobacco Cessation Health Systems Change for Tobacco Dependence Treatment and Lung Cancer Screening"
$100,000 (annual total); 10% effort

NIEHS P30 ES020957 (PI: Runge-Morris)
Center for Urban Responses to Environmental Stressors (CURES)
1,539,440; 8% effort
9/30/2017-9/29/2022

Role: Leader, Environment and Cancer

GTDR 14299438 Komen for the Cure Graduate Training in Breast Cancer Disparities Research (PI: Cote)
"Multidisciplinary training in the biology of breast cancer disparities"
10/1/2014-2/26/2021
$405,000 (total direct); 2% effort

1 F31 CA221333-01 (PI: Shaik; Dr. Cote was primary mentor on this award)
"Characterizing novel radiologic and pathologic tissue-based risk factors for breast cancer in African American women with benign breast disease."
9/11/2017-6/30/2018

R21CA184778 (PI: Schwartz)
"Profiling Genetic Alterations in NSCLC in African Americans"
$87,068 (annual direct); 2% effort
9/11/2014-8/31/2016

Komen for the Cure Foundation (PI: Cote)
IIRG 222547
"Benign Breast Disease and the Risk of Breast Cancer: The Detroit Cohort"
$789,463 (direct); 30% effort
7/28/2012-7/27/2016, extensions and additional support through 2019

NCI R01 CA142081 (PI: Schilkraut)
"Epidemiology of Ovarian Cancer in African American Women"
$499,542 (direct); Role: Co-Investigator, 9% effort
6/2010-5/2016

NCI R01 CA97075-08 (PI: Petersen, Site PI: Schwartz)
"Pancreatic Cancer Genetic Epidemiology Consortium"
$365,011 (direct); Role: Collaborator, 0% effort
6/2008-5/2013

Mass General Hospital (site PI: Cote)
"Impact of Smoking Cessation and Screening on Michigan's Lung Cancer Rate"
$21,147 (direct); 2% effort, no cost

NCI R21CA1543219-01 (MPI: Sheng and Lonardo)
"Assessment of maspin expression in NSCLC and its interaction with HDAC"
$275,000 (direct); Role: Collaborator, 0% effort
6/1/10-5/31/2012

NIH/NHLBI-Women's Health Initiative
"Midwestern Regional Extension"
100 hours annually, Role: Investigator

4/1/2010-9/30/2018

Department of Defense/NOMIC/KCI (PI: Cote)
"Molecular Signatures of non-small Cell Lung Cancers: Oncogenes as Therapeutic Targets"
$50,000 (total); 0% effort
7/1/2010-6/30/2011

NCI 3K07 CA125203-02S1 American Recovery and Reinvestment Supplement (PI: Cote)
"Exploring Common Linkage Regions in Lung Cancer and COPD"
$99,522 (direct); 0% effort
9/2009-9/2011

NCI K07 CA125203-01A2 Mentored Career Development Award (PI: Cote)
"Exploring Common Linkage Regions in Lung Cancer and COPD"
$615,375 (direct); 75% effort
9/2008-2/2014

National Lung Cancer Partnership/LUNGevity Foundation
Career Development Award (PI: Cote)
"Hormonal Factors and Lung Cancer: A Potential Target for Therapy"
$100,000 (total); 35% year 1, 50% year 2
3/2007-3/2009

Institute for Population Studies, Health Assessment, Administration, Services and Economics (PIs: Cote and Rybicki)
"Risk Factors Associated with Racial Disparities in Endometrial Cancer Survival"
$73,098 (total); 0% effort
4/2007-10/2008

NCI R01 CA97075 (PI: Petersen)
"Pancreatic Cancer Genetic Epidemiology Consortium"
$6,589,472 (total); Role: Co-Investigator, 5%
8/2002-7/2007

PUBLICATIONS

Peer-Reviewed Publications (*indicates trainee)

Reports of Original Work

1. Lawson AB, Kim J, Johnson C, Ratnapradipa KL, Alberg AJ, Akonde M, Hastert T, Bandera EV, Terry P, Mandle H, **Cote ML**, Bondy M, Marks J, Peres LC, Schildkraut J, Peters ES. The association between mediated deprivation and ovarian cancer survival among African American women. Cancers (Basel). 2023 Oct 4;15(19):4848. doi: 10.3390/cancers15194848. PMID: 37835542

2. Kumar B, Khatpe AS, Guanglong J, Batic K, Bhat-Nakshatri P, Granatir MM, Addison RJ, Szymanski M, Baldridge LA, Temm CJ, Sandusky G, Althouse SK, **Cote ML**, Miller KD, Storniolo AM, Nakshatri H. Stromal heterogeneity may explain increased incidence of metaplastic breast cancer in women of African descent. Nat Commun. 2023 Sep 14;14(1):5683. doi: 10.1038/s41467-023-41473-6. PMID: 37709737

3. Johnson CE, Alberg AJ, Bandera EV, Peres LC, Akonde M, Collin LJ, **Cote ML**, Hastert TA, Hébert JR, Peters ES, Qin B, Terry P, Schwartz AG, Bondy M, Epstein MP, Mandle HB, Marks JR, Lawson AB, Schildkraut JM. Association of inflammation-related exposures and ovarian cancer survival in a multi-site cohort study of Black women. Br J Cancer 2023 Oct;129(7):1119-1125. doi: 10.1038/s41416-023-02385-w. PMID: 37537254

4. Lawson AB, Kim J, Johnson C, Hastert T, Bandera EV, Alberg AJ, Terry P, Akonde M, Mandle H, **Cote ML**, Bondy M, Marks J, Peres L, Ratnapradipa KL, Xin Y, Schildkraut J, Peters ES. Deprivation an dsegregation in ovarian cancer survival among African American women: a mediation analysis. Ann Epidemiol. 2023 Oct;86:57-64. doi: 10.1016/j.annepidem.2023.07.001. PMID: 37423270

5. Wharram CE*, Kyko JM, Ruterbusch JJ, Beebe-Dimmer JL, Schwartz AG, **Cote ML**. Use of electronic cigarettes among African American cancer survivors [published online ahead of print, 2023 Jul 3]. *Cancer*. 2023;10.1002/cncr.34933. doi:10.1002/cncr.34933

6. Mullins MA*, Ruterbusch J, **Cote ML**, Uppal S, Wallner LP. Trends in hospice referral timing and location among individuals dying of ovarian cancer: persistence of missed opportunities. Int J Gynecol Cancer. 2023 May 19:ijgc-2023-004405. Doi: 10.1136/ijgc-2023-004405. PMID: 37208020.

7. Banning K*, Fucinari J, Fielder A*, Ruterbusch JJ, Beebe-Dimmer JL, Schwartz AG, Wallbillich JJ, **Cote ML**. Quality of life in endometrial cancer survivors by grade of disease. Cancer Med. 2023 May 26. Doi: 10.1002/cam4.5987 PMID: 37148545.

8. Schildkraut JM, Johnson C, Dempsey LF, Qin B, Terry P, Akonde M, Peters ES, Mandle H, **Cote ML**, Peres L, Moorman P, Schwartz AG, Epstein M, Marks J, Bondy M, Lawson AB, Alberg AJ, Bandera EV. Survival of epithelial ovarian cancer in Black women: a society to cell approach in the African American cancer epidemiology study (AACES). Cancer Causes Control. 2022 Dec 15:1-15. doi: 10.1007/s10552-022-01660-0. PMID: 36520244.

9. Mattei LH*, Robb L, Banning K, Polan RM, **Cote ML**. Enrollment of individuals from racial and ethnic minority groups in gynecologic cancer precision oncology trials. Obstet Gynecol. 2022 Oct 1;140(4):654-661. doi: 10.1097/AOG.0000000000004917. Epub 2022 Sep 7. PMID: 36075065.

10. Nolin AC, Tian C, Hamilton CA, Casablanca Y, Bateman NW, Chan JK, **Cote ML**, Shriver CD, Powell MA, Phippen NT, Conrads TP, Maxwell GL, Darcy KM. Conditional estimates for uterine serous cancer: Tools for survivorship counseling and planning. Gynecol Oncol. 2022 Jul;166(1):90-99. doi: 10.1016/j.ygyno.2022.05.013. Epub 2022 May 24. PMID: 35624045.

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12. Peres LC, Colin-Leitzinger C, Sinha S, Marks JR, Conejo-Garcia JR, Alberg AJ, Bandera EV, Berchuck A, Bondy ML, Christensen BC, **Cote ML**, Doherty JA, Moorman PG, Peters ES, Moran Segura C, Nguyen JV, Schwartz AG, Terry PD, Wilson CM, Fridley BL, Schildkraut JM. Racial Differences in the Tumor Immune Landscape and Survival of Women with High-Grade Serous Ovarian Carcinoma. Cancer Epidemiol Biomarkers Prev. 2022 May 4;31(5):1006-1016. doi: 10.1158/1055-9965.EPI-21-1334.PMID: 35244678

13. McBride CM, Pathak S, Johnson CE, Alberg AJ, Bandera EV, Barnholtz-Sloan JS, Bondy ML, **Cote ML**, Moorman PG, Peres LC, Peters ES, Schwartz AG, Terry PD, Schildkraut JM. Psychosocial factors associated with genetic testing status among African American women with ovarian cancer: Results from the African American Cancer Epidemiology Study. Cancer. 2022 Mar 15;128(6):1252-1259. doi: 10.1002/cncr.34053. Epub 2021 Dec 9.PMID: 34882782

14. Corey L*, **Cote ML**, Ruterbusch JJ, Winer I. Disparities in adjuvant treatment of high grade endometrial cancer in the Medicare population. Am J Obstet Gynecol. 2021 Nov 1:S0002-9378(21)01179-0. doi: 10.1016/j.ajog.2021.10.031

15. Blackford AL, Childs EJ, Porter N, Petersen GM, Rabe KG, Gallinger S, Borgida A, Syngal S, **Cote ML**, Schwartz AG, Goggins MG, Hruban RH, Parmigiani G, Klein AP. A risk prediction tool for individuals with a family history of breast, ovarian or pancreatic cancer: BRCAPANCPRO. Br J Cancer. 2021 Oct 26. doi: 10.1038/s41416-021-01580-x.

16. Mullins MA*, Uppal S, Ruterbusch JJ, **Cote ML**, Clarke P, Wallner LP. Physician influence on variation of receipt of aggressive end-of-life care among women dying of ovarian cancer. JCO Oncol Pract. 2021 Sep 28:OP2100351. doi: 10.1200/OP.21.00351.

17. Shallal A, Abada E, Musallam R, Fehmi O, Kaljee L, Fehmi Z, Alzouhayli S, Ujayli D, Dankerlui D, Kim S, **Cote ML**, Kumar VA, Zervos M, Ali-Fehmi R. Evaluation of Covid-19 vaccine attitudes among Arab American health care professionals living in the United States. Vaccines (Basel). 2021 Aug 24;9(9):942. doi: 10.3390/vaccines9090942.

18. Corey L*, Fucinari J, Elshaikh M, Schultz D, Musallam R, Zaiem F, Daaboul F, Fehmi O, Dyson G, Ruterbusch J, Morris R, **Cote ML**, Ali-Fehmi R, Bandyopadhyay S. The impact of positive

cytology in uterine serous carcinoma: A reassessment. Gynecol Oncol Rep. 2021 Jul 12;37:100830. doi: 10.1016/j.gore.2021.100830.

19. Fucinari J, Elshaikh MA, Ruterbusch JJ, Khalil R, Dyson G, Shultz D, Ali-Fehmi R, **Cote ML**. The impact of race, comorbid conditions and obesity on survival endpoints in women with high grade endometrial carcinoma. Gynecol Oncol. 2021 May 10:S0090-8258(21)00356-5. doi: 10.1016/j.ygyno.2021.04.036.

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27. Conner KL*, Shaik AN, Ekinci E, Kim S, Ruterbusch JJ, **Cote ML**, Patrick SM. HPV indication of APOBEC3 enzymes mediate overall survival and response to cisplatin in head and neck cancer. DNA Repair 2020 Mar; 87:102802.

28. Nagasaka M, Lehman A, Chlebowski R, Haynes BM, Ho G, Patel M, Sakoda LC, Schwartz AG, Simon MS, **Cote ML**. COPD and lung cancer incidence in the Women's Health Initiative Observational Study: A brief report. Lung Cancer. 2020 Mar;141:78-81.

29. Schabath MB and **Cote ML**. Cancer Progress and Priorities: Lung Cancer. Cancer Epidemiol Biomarkers Prev. 2019 Oct;28(10):1563-1579.

30. Wong C, Chen F, Alirezaie N, Wang Y, Cuggia A, Borgida A, Holter S, Lenko T, Domecq C; Alzheimer's Disease Neuroimaging Initiative, Petersen GM, Syngal S, Brand R, Rustgi AK, **Cote ML**, Stoffel E, Olson SH, Roberts NJ, Akbari MR, Majewski J, Klein AP, Greenwood CMT, Gallinger S, Zogopoulos G. A region-based gene association study combined with a leave-one-out sensitivity analysis identifies SMG1 as a pancreatic cancer susceptibility gene. PLoS Genet. 2019 Aug 30;15(8):e1008344. doi: 10.1371/journal.pgen.1008344. eCollection 2019 Aug.

31. Manichaikul A, Peres LC, Wang XQ, Barnard ME, Chyn D, Sheng X, Du Z, Tyrer J, Dennis J, Schwartz AG, **Cote ML**, Peters E, Moorman PG, Bondy M, Barnholtz-Sloan JS, Terry P, Alberg AJ, Bandera EV, Funkhouser E, Wu AH, Pearce CL, Pike M, Setiawan VW, Haiman CA; African American Breast Cancer Consortium (AABC); African Ancestry Prostate Cancer Consortium (AAPC), Palmer JR, LeMarchand L, Wilkens LR, Berchuck A, Doherty JA, Modugno F, Ness R, Moysich K, Karlan BY, Whittemore AS, McGuire V, Sieh W, Lawrenson K, Gayther S, Sellers TA, Pharoah P, Schildkraut JM; African American Cancer Epidemiology Study (AACES) and the Ovarian Cancer Association Consortium (OCAC). Identification of novel epithelial ovarian cancer loci in women of African ancestry. Int J Cancer. 2019 Aug 30. doi: 10.1002/ijc.32653.

32. Mullins MA*, Peres LC, Alberg AJ, Bandera EV, Barnholtz-Sloan JS, Bondy ML, Funkhouser E, Moorman PG, Peters ES, Terry PB, Schwartz AG, Lawson AB, Schildkraut JM, **Cote ML**. Perceived discrimination, trust in physicians, and prolongs symptom duration before ovarian cancer diagnosis in the African American Cancer Epidemiology Study. Cancer 2019 Aug 30 doi: 10.1002/ijc.32653.

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Way JB, Monteiro AN, Levine DA, Setiawan VW, Haiman CA, LeMarchand L, Wilkens LR, Karlan BY, Menon U, Ramus S, Gayther S, Gentry-Maharaj A, Terry KL, Cramer DW, Goode EL, Larson MC, Kaufmann SH, Cannioto R, Odunsi K, Etter JL, Huang RY, Bernardini MQ, Tone AA, May T, Goodman MT, Thompson PJ, Carney ME, Tworoger SS, Poole EM, Lambrechts D, Vergote I, Vanderstichele A, Van Nieuwenhuysen E, Anton-Culver H, Ziogas A, Brenton JD, Bjorge L, Salvensen HB, Kiemeney LA, Massuger LFAG, Pejovic T, Bruegl A, Moffitt M, Cook L, Le ND, Brooks-Wilson A, Kelemen LE, Pharoah PDP, Song H, Campbell I, Eccles D, DeFazio A, Kennedy CJ, Schildkraut JM. Evaluation of vitamin D biosynthesis and pathway target genes reveals UGT2A1/2 and EGFR polymorphisms associated with epithelial ovarian cancer in African American women. Cancer Med. 2019 May;8(5):2503-2513.

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Review Articles

1. Gadgeel SM, **Cote ML**, Schwartz AG, Matherly LH, Wozniak A, Bepler G. Parameters for individualizing systemic therapy in non-small cell lung cancer. Drug Resis Update. 2010 Nov 2 PMID: 21051275

2. Schwartz AG, Prysak GM, Bock CH, **Cote ML**. The Molecular Epidemiology of Lung Cancer. Carcinogenesis 2007; March; 28(3): 507-18.

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Book Authorships, Editorships, and Chapters

1. **Cote ML** and Ramnath N. "Incidence, Behavior, and Therapy of Lung Cancer in Women" American Society of Clinical Oncology 2010 Educational Book. ASCO, 2010.

2. **Cote ML**. "Study designs in genetic epidemiology". Tumor Biomarker Discovery: Methods and Protocols. Editor: Tainsky MA. Humana Press, 2009.

Other (not peer-reviewed)

1. **Cote ML**. "Lung Cancer: An update on the search for a gene" Michigan Cancer Consortium Update (Newsletter), November 2008.

2. **Cote ML**. "For the 'greater good' would you share your biological data? Science's need for study participants' consent" BioMed Central Blog, September 2014.

PRESENTATIONS

Podium Presentations (refereed, *trainee)

1. Shaik, AN*…Cote, ML. Adipose inflammation and the risk of benign and malignant breast disease in African American women. AACR Annual Meeting, Late Breaking Abstract Minisymposium, Chicago, IL, April 2018.

2. Cote, ML. Risk factors for endometrial cancer in black and white women: a pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2). AACR Annual Meeting, Minisymposium, Washington, DC, April 2013.

Poster Presentations (refereed, *trainee)

1. Holowatyj AN*, Ruterbusch JJ, Ali-Fehmi R, Bandyopadhyay S, Mehner C, Stallings Mann M, Dyson G, Radisky D, Cote ML. Expression profiling of paired benign and breast cancer lesions in African American women. American Association for Cancer Research (AACR) Annual Meeting, April 2017.

2. Shaik AN*, Ruterbusch JJ, Abdulfatah E, Alosh B, Pardeshi V, Ali-Fehmi R, Visscher DW, Bandyopadhyay S, Cote ML. Fibroadenomas on benign breast biopsy and subsequent breast cancer risk in an African American Cohort. American Association of Cancer Research Molecular Working Group Special Conference, November 2016.

3. Ruterbusch JJ, Cote ML, Boerner J, Abdulfatah E, Alosh B, Pardeshi V, Roquiz W, Ali-Fehmi R, Bandyopadhyay. Breast cancer subtype subsequent to a benign breast biopsy among African Americans. American Association of Cancer Research Molecular Working Group Special Conference, November 2016

4. Cote ML, Chen W, Ruterbusch JJ, Abdulfatah E, Alosh B, Pardeshi V, Shaik AN, Visscher DW, Bandyopadhyay, Ali-Fehmi R. Benign breast disease and subsequent breast cancer risk: The Detroit Cohort. American Association of Cancer Research Molecular Working Group Special Conference, November 2016

5. Holowatyj AN*, Ruterbusch JJ, Ali-Fehmi R, Bandyopadhyay S, Dyson G, Radisky D, Cote ML.Transcriptional variations associated with time to breast cancer development among African American women with benign breast disease. 24th BIENNIAL CONGRESS OF THE EUROPEAN ASSOCIATIONFOR CANCER RESEARCH: JUL. 2016

6. Holowatyj AN*, Ali-Fehmi R, Ruterbusch JJ, Abdulfatah E, Pardeshi V, Roquiz W, Alosh B, Bandyopadhyay S, Radisky D. Cote ML. Ankryin repeat domain 30A as a novel molecular marker of columnar alterations in benign breast disease and subsequent breast cancer in African American women. American Association for Cancer Research (AACR) Annual Meeting, New Orleans, LA, 2016.

7. Cote ML, Ruterbusch JJ, Bandyopadhyay S, Ahmed Q, Alosh B, Abdulfatah E, Arabi H, Ali-Fehmi R. Characteristics of benign breast disease and subsequent risk of breast cancer differ by age among African Americans. AACR-San Antonio Breast Cancer Symposium, San Antonio, TX, 2014.

8. Cote ML, Ruterbusch JJ, Lu K, Olson SH, Ali-Fehmi R. Racial disparities in aggressive endometrial cancer incidence and mortality are limited to non-Hispanic black women. AACR Special Conference on Health Disparities, San Antonio, TX, 2014.

9. Cote ML, Ruterbusch JJ, Chen W, Bandyopadhyay S, Ahmed Q, Alosh B, Abdulfatah E, Radisky DC, Frost MH, Degnim AC, Hartmann LC, Visscher DW, Ali-Fehmi R. Racial differences in benign breast disease features. SIS World Congress on Breast Healthcare, Orlando, FL, 2014.

10. Mitro SD*, Ali-Fehmi R, Bandyopadhyay S, Alosh B, Albashiti B, Radisky DC, Frost MH, Degnim AC, Ruterbusch JJ, Cote ML. Clinical characteristics of breast cancers in African-American women with benign breast disease: A comparison to the Surveillance, Epidemiology and End Results Program. AACR Special Conference on Health Disparities, Atlanta, GA, 2013.

11. Haynes B*, Ruterbusch JJ, Simon M, Cote ML. A comparison of hormone receptor status in black women born in the U.S., West Africa, East Africa and the Caribbean- a SEER Analysis. AACR San Antonio Breast Cancer Symposium, San Antonio, TX, 2013.

12. Wang A, Kubo J, Luo J, Desai M, Henderson M, Chlebowski R, Tindle H, Chen C, Gomez S, Manson JE, Schwartz AG, Wactawski-Wende J, Cote ML, Patel M, Stefanick ML, and Wakelee HA. Active and passive smoking in relation to lung cancer incidence in the Women's Health Initiative prospective cohort study. American Society of Clinical Oncology, Chicago, IL, 2013.

13. Gadgeel S, Bollig-Fischer A, Cote ML, Schwartz AG, Land S, Wenzlaff A, Mantha L, Wozniak A, Sukari A, Chen Wei, Bepler G. Multiplex testing of driver mutations in non-small cell lung cancer (NSCLCs) of African-American (AA) patients. American Society of Clinical Oncology, Chicago, IL, May 2013.

14. Vigneau FD, and Cote ML. Usefulness of Collaborative Stage (CS) Site Specific Factors (SSF) 3, 4, 5 and 6 in describing short-term mortality risk disparities for Type II Endometrial Cancers in Metropolitan Detroit. North American Association of Cancer Registries, Austin, TX, 2013.

15. Bandyopadhyay S, Alosh B, Bowles M, Cote M, Shi D, Salem N, Kim MH, Visscher D, Ali-Fehmi R. Clinico-Pathological Features of Fibroadenoma Occurring in a Cohort of Young African American Patients: Single Institution Experience. United States & Canadian Academy of Pathology Annual Meeting, Baltimore, MD, 2013.

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17. Gadgeel SM, Cote ML, Bepler G, Murphy V, Malysa A, Wozniak AJ, Sukari A, Schwartz AG. Frequency of anaplastic lymphoma kinase (ALK) positive tumors among African American non-small cell lung cancer (NSCLC) patients. American Society of Clinical Oncology, Chicago, IL, May 2012. J Clin Oncol 30, 2012 (suppl; abstr 7593).

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19. Bandyopadhyay S, Cote ML, Visscher DW, Ruterbusch JJ, Albashiti B, Alosh B, Frost MH, Hartmann LC, Ali-Fehmi R. Expression of selective predictive markers in African American women with atypical hyperplasia of the breast. San Antonio Breast Cancer Symposium, San Antonio, TX, December 2011.

20. Ali-Femhi R, Cote ML, Ruterbusch JJ, Alosh B, Bandyopadhyay S, Albashiti B, Hartmann LC, Frost MH, Visscher DW. Benign breast disease and breast cancer in African American women. San Antonio Breast Cancer Symposium, San Antonio, TX, December 2011.

21. Patel DA, Saraiya M, Copeland G, Cote ML, Datta SD, Sawaya GF. Treatment patterns for cervical cancer in situ in Michigan, 1998-2003. International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 2011.

22. Cote ML, Atikukke G, Ruterbusch JJ, Olson SH, Sealy-Jefferson S, Rybicki BA, Hensley-Alford S, Elshaikh MA, Gaba AR, Schultz D, Ali-Fehmi R, Haddad R, Munkarah AR. Oncogene mutations in endometrial cancer vary by race. AACR Annual Conference, Orlando, Florida, April 2011.

23. Cote ML, Ruterbusch JJ, Olson SH, Sealy-Jefferson S, Rybicki BA, Hensley-Alford S, Elshaikh MA, Gaba AR, Schultz D, Ali-Fehmi R, Munkarah AR. Race is a predictor for endometrioid endometrial cancer cause-specific survival, but not all-cause survival. AACR Special Conference on Health Disparities, Miami, Florida, October 2010.

24. Atikukke G, Cote ML, Edwards DJ*, Gadgeel S, Soubani AO, Lonardo F, Schwartz AG, Ethier SP, Haddad R. EGFR mutations in African American NSCLC patients occurs at a similar frequency to Caucasians but demonstrates an extreme bias to exon 19 mutations. AACR Special Conference on Molecular Diagnostics in Cancer Therapeutic Development, Denver, Colorado. September 2010.*This abstract was selected for a press release by AACR as a highlighted abstract.

25. Gadgeel SM, Goveas R, Vigneau FD, Quarshie WO, Islam MK, Schwartz AG, Wozniak AJ, Cote ML. "Brain Metastases in lung cancer patients: Analysis of the Detroit Surveillance, Epidemiology and End Results (SEER) Data. American Society of Clinical Oncology, Chicago, Illinois. June 2010.

26. Atikukke G, Cote ML, Schwartz AG, Gadgeel SM, Soubani AO, Lonardo F, Haddad R. "Oncogenomic profiling of NSCLC: A pilot study" AACR Annual Meeting, Washington, D.C. April 2010.

27. Cote ML, Schwartz AG, Gadgeel S, Soubani AO, Haddad R. Oncogenomic profiling of adenocarcinomas: a pilot study. AACR/IASLC Special Conference on Lung Cancer. Coronado, California. January 2010.

28. Patel MK*, Cote ML, Ali-Fehmi R, Munkarah AR, Kim W, Elshaikh MA. Trends in the Utilization of Adjuvant Vaginal Cuff Brachytherapy and/or External Beam Radiation Treatment in Stage I and II Endometrial Cancer: A Surveillance, Epidemiology and End-Results (SEER) Study. American Society for Radiation Oncology Annual Meeting. Chicago, Illinois. November 2009.

29. Nyhuis M, Petrucelli N, Barrick M, Abrams J, Cote M, Hammad N, Simon, M. The accuracy of the CancerGene program to assess the probability of a BRCA1/2 mutation: The impact of limited family structure. National Society of Genetic Counselors Annual Meeting. Atlanta, Georgia, November 2009.

30. Schwartz AG, Cote ML, Wenzlaff AS, Land SL, Amos CI. Racial differences in lung cancer risk associated with SNPs on 15q25 and variation in LD patterns. GENETIC EPIDMIOLOGY 32(7): 152. International Genetic Epidemiology Society, St. Louis, Missouri, September, 2008.

31. Sealy-Jefferson, S*, Schenk, M.J., Cote ML. A Population-Based Analysis of Race and gender differences in pancreas cancer survival. American Association of Cancer Research Special Conference on Racial and Health Disparities. Atlanta, Georgia, November 2007.

32. Cote, ML, Orom H, Wenzlaff, A.G., Schwartz A.G. Ascertaining first-degree relatives in adult-onset cancer research: The genetic epidemiology of lung cancer study, 1999-2003. American Association of Cancer Research Special Conference on Racial and Health Disparities. Atlanta, Georgia, November 2007.

33. Ali-Fehmi, R. Cote, ML., Arabi, M.H., Bryant, C.S., Shah, J.P., Mughrabi, L., Schimp, V.L., Sauder, K., Abdul-Karim, F., Munkarah, A.R. Endometrial carcinoma (EC) in Women 35 years of age or younger. United States and Canadian Academy of Pathology. San Diego, California, March 2007.

34. Bock C.H., Wenzlaff A.S., Cote ML., Land S.J., Schwartz, A.G. NQ01 genotype and risk of early-onset lung cancer: Results from a population-based study. PROC AMER ASSOC CANCER RES. Washington, DC. April 2006.

35. Cote ML., Wenzlaff A.S., Bock C.H., Land S.J., Santer S.K., Schwartz D.R., Schwartz, A.G. CYP1A1 and CYP1B1 polymorphisms and risk of early-onset lung cancer: a population-based study. PROC AMER ASSOC CANCER RES. Washington, DC. April 2006.

36. Ali-Fehmi, R, Cote, ML, Schimp, V.L., Munkarah, A.R. Leiomyosarcoma of the uterus: A population-based analysis. Society of Gynecologic Oncologists. Palm Springs, CA. March 2006.

37. Cote, ML., Schimp, V.L., Wenzlaff, A.J., Munkarah, A.R. Second primary cancers after an endometrial cancer diagnosis: a population-based study. AACR Frontiers in Cancer Prevention Research. Baltimore, MD. October 2005.

38. Schwartz, A.G., Wenzlaff, A.J., Cote, ML., Schwartz, D.R., Land, S.J., McKeigue, P.M. Identification of lung cancer susceptibility regions using admixture mapping in an African American population. PROC AMER ASSOC CANCER RES. Orange County, CA. April 2005.

39. Cote, ML., Wenzlaff, A.J., Schwartz, A.G. Secondary cancers after a lung carcinoid diagnosis: a population-based study. PROC AMER ASSOC CANCER RES. Orange County, CA. April 2005.

40. Cote, ML., Kardia, S.L.R., Schwartz, A.G. Racial Differences in Early Onset Lung Cancer Risk by CYP1B1*3 Genotype. AACR Special Conference: SNPs, Haplotypes, and Cancer: Applications in Molecular Epidemiology. Miami, Florida, September 2003.

41. Spindler, A., Cote, M., Miller, N., Santer, S., Schwartz, A.G. Survival Differences in Individuals with Early-Onset Lung Cancer Associated with a CYP1B1 Polymorphism. PROC AMER ASSOC CANCER RES. San Francisco, CA. April 2003.

42. Cote, ML., Kardia, S.L.R., Spindler, A.J., Schwartz, A.G. Racial Differences in Elevated Cancer Risk among Relatives of Early Onset Lung Cancer Cases. GENETIC EPIDEMIOL, 23, 274, 2002.

43. Schwartz, A.G., Spindler, A., Cote, M., Miller, N. CYP1A1, CYP2E1 AND CYP1B1 and Risk of Early Onset Lung Cancer. PROC AMER ASSOC CANCER RES 43: 401, 2002.

Invited Lectures/Presentations
International/National

1. Somatic Mutations in High Grade Endometrial Cancers: Old Challenges and New Targets. Baylor University, Duncan Cancer Center, Cancer Prevention and Population Sciences Seminar Series. Virtual, January 19, 2023.

2. Risk of Breast Cancer in Women with Benign Breast Disease: Novel Pathological Insights. Simon Comprehensive Cancer Center, Indianapolis, IN, Vera Bradley Breast Cancer Research Foundation Seminar Series. April 28, 2022

3. Somatic Mutations in High Grade Endometrial Cancers: Old Challenges and New Targets. Georgetown Cancer Center, Cancer Control and Prevention meeting. Virtual, April 25, 2022

4. Somatic Mutations in High Grade Endometrial Cancers: Old Challenges and New Targets. Knight Cancer Center, Population Sciences Program meeting. Virtual, January 25, 2022

5. Somatic Mutations in High Grade Endometrial Cancers: Old Challenges and New Targets. Moffitt Cancer Center, Grand Rounds in Population Science. Virtual, October 14, 2021

6. Somatic Mutations in High Grade Endometrial Cancers. National Cancer Institute SeqSPACE Webinar, Virtual, October 12, 2021

7. Beyond Obesity: The Increasing Incidence and Epidemiology of High Grade Endometrial Cancers. Center for Cancer Health Equity (CCHE) at the Cancer Institute of New Jersey, Rutgers University Distinguished Lecturer Series. Virtual, May 24, 2021

8. Beyond Obesity: The Increasing Incidence and Epidemiology of High Grade Endometrial Cancers. Case Western University Cancer Seminar Series Cancer Prevention, Control & Population, Virtual, February 26, 2021

9. Obesity and Arab Americans. The National Arab American Medical Association Meeting, Virtual, October 24, 2020.

10. Benign Breast Disease and Subsequent Risk of Breast Cancer: Novel Molecular Insights. University of Michigan Population Science Program Meeting, Ann Arbor, MI, April 2019.

11. Eliminating Disparities: Reject Common Dogma. University of Cincinnati Cancer Center Annual Conference, Cincinnati, OH, June 2018.

12. Benign Breast Disease and Subsequent Risk of Breast Cancer: The Detroit Cohort. NCI New Grantee Workshop. Rockville, MD, September 2017.

13. Benign Breast Disease and Subsequent Risk of Breast Cancer: The Detroit Cohort. Columbia University Mailman School of Public Health. New York City, NY, April 2017.

14. Molecular Classification of High Grade Endometrial Cancers: Extending TCGA Findings to a Diverse Population. Advances in Endometrial Cancer Epidemiology and Biology Symposium. NCI-R13 funded symposium, Memorial Sloan Kettering Cancer Center, NYC, NY, March 2016.

15. Breast and endometrial cancers: An emerging public health crisis associated with obesity. 7th International Conference on Health Issues in Arab Communities. Muscat, Oman, March 2015.

16. Endometrial cancer: Epidemiology, Etiology, and Emerging Research Challenges. University of Colorado, Denver, Reproductive Biology Program, Aurora, Colorado, January 2015.

17. Recent Progress in Lung Cancer Epidemiology, Etiology, and Screening. Epidemiology Seminar Series, University of Alabama, Birmingham, School of Public Health, Birmingham, Alabama, October 2014.

18. Benign Breast Disease and Subsequent Breast Cancer Risk: Expanding Disparities Research. Cancer. Cancer Prevention Grand Rounds, MD Anderson Cancer Center, Houston, Texas, August 2014.

19. Risk factors in African American Women. Advances in Endometrial Cancer Epidemiology and Biology Symposium. NCI-R13 funded symposium, Harvard School of Public Health, Cambridge, MA, March 2014.

20. Benign Breast Disease and Subsequent Breast Cancer Risk: Expanding Disparities Research. Cancer Biology Program, Mayo Clinic—Jacksonville, Florida, March 2014.

21. Lung cancer in women: Beyond smoking. Thailand National Cancer Institute National Cancer Forum 2013. Bangkok, Thailand, August 2013.

22. Epidemiology and the Environment: Methods to study exposure-disease associations in humans. Khon Kaen University, Khon Kaen, Thailand, October 2012

23. Cancer Registries. National Cancer Institute (Thailand) 11th Annual Conference, Bangkok, Thailand, March 2012.

24. Lung Cancer Epidemiology: Beyond Tobacco. Walailak University, Nakhon Si Thammarat, Thailand, March 2012.

25. Allocating Resources for Identification of Cancer Risk in Individuals, Families and Populations. Translational Cancer Prevention and Biomarkers Workshop, Bangalore, India, February 2011.

26. Frequency and Type of EGFR Mutations in African Americans with Non-small Cell Lung Cancer. National Functional Genomics Center 2010 Annual Meeting, Clearwater, Florida, October 2010.

27. Hormone Receptors and Lung Cancer: A potential target for therapy? National Lung Cancer Partnership Annual Meeting, Orlando, Florida, May 2009

28. Lung Cancer. National Society for Genetic Counselors Annual Educational Meeting, Nashville, Tennessee, November 2006.

29. Around People: Epidemiology in Everyday Life. National Society for Genetic Counselors Annual Educational Meeting, Nashville, Tennessee, November 2006.

30. Racial differences in familial aggregation of lung and other cancers. American College of Chest Physicians 72nd Annual International Scientific Assembly, Salt Lake City, UT, October 2006.

31. Lung Cancer Epidemiology: Defining a High Risk Group. Mt. Sinai Hospital, New York City, New York, April 2006.

32. Lung Cancer Risk in Relatives of Early Onset Cases. Presented at the Thomas L. Petty Aspen Lung Conference. Aspen, Colorado, June, 2003.

33. Tobacco smoke and childhood illness. Presented at the Maternal Infant and Child Health Workshop, Atlanta, Georgia, December 1998.

Local/Regional

34. Work-Life Balance. Coalition for Women in Science, Technology, Engineering, and Mathematics (CW STEM) Mentoring Lunch Series, Wayne State University, Detroit, MI, February 26, 2016.

35. Molecular Epidemiology and Pathology: A Successful Partnership. Pathology Research Retreat, Detroit, MI, December 2015.

36. Benign Breast Disease and Subsequent Breast Cancer Risk in African Americans. Wayne State University Department of Pathology Seminar Series, Detroit, MI, September 2014.

37. Recent progress in lung cancer epidemiology, etiology, and screening. Wayne State University Department of Family Medicine and Public Health Practice Lunch Seminar Series, Detroit, MI, September 2014.

38. Cancer Disparities: Challenges and Opportunities in the WHI. Midwestern Regional Conference, Chicago, IL, July 2012.

39. Germline and somatic mutations as predictors of risk and response in NSCLC. Department of Pharmaceutical Sciences, Wayne State University, Seminar Series, 2011

40. Germline and Somatic Mutations as Predictors of Risk and Prognosis in Lung Cancer. Karmanos Cancer Institute Clinical Cancer Genetics Grand Rounds, Detroit, Michigan, January 2010.

41. Hormone Receptors and Lung Cancer: A potential target for therapy? Henry Ford Health System Cancer Genetics Grand Rounds, Detroit, Michigan, October 2009.

42. Mentoring in Math, Science and Health. Young Women, Strong Leaders Conference, sponsored by the State of Michigan, Detroit, Michigan, April 2009.

43. Racial differences in endometrial cancer survival. Wayne State University Conference on Racial and Ethnic Disparities in Health Biannual Meeting. Detroit, Michigan, November 2007.

44. Racial differences in endometrial cancer survival: The INPHAASE Study. University of Michigan Cancer Epidemiology Working Group. Ann Arbor, Michigan, April 2007.

45. Lung Cancer Epidemiology: Defining a High Risk Group. VA Tumor Board. Detroit, Michigan, August 2006.

46. Lung Cancer Epidemiology: Beyond Smoking. National Cancer Registrars Week. Detroit, Michigan, April, 2006.

47. Lung Cancer Epidemiology: Defining a High Risk Group. Michigan State University, East Lansing, Michigan, March, 2006.

48. Tobacco and Genetics: Current Challenges and Future Directions. Michigan Department of Community Health. Lansing, Michigan, October, 2005.

49. The Genetic Epidemiology of Lung Cancer. Cancer Genomics in Public Health. Okemos, Michigan, June, 2005.

Appendix B: Additional Materials Considered

ADDITIONAL MATERIALS CONSIDERED

1. J&J Media Statement on Discontinuation of North America Talc Sales (May 19, 2020)

2. J&J Media Statement on Discontinuation of Worldwide Talc Sales (August 11, 2022)

3. Reuters, J&J to End Global Sales of Talc-Based Baby Powder (August 11, 2022)

4. Cosmetics Design USA, J&J Will Stop Selling Talc in US and Canada (May 20, 2020)

5. AMA Analytical Services Inc., Summary of Analysis (October 11, 2019)

6. Amphibole Asbestos Found in Historical Johnson's Baby Powder 1960 – 2000s

7. Health Canada Talc Poster

8. IARC Monograph 100C, (Arsenic, Metals, Fibres, and Dusts V100C, A Review of Human Carcinogens - 2012)

9. IARC Monograph Priorities, Advisory Group recommendations on priorities for the IARC Monographs (April 17, 2019)

10. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans V93, Carbon Black, Titanium Dioxide, and Talc, IARC Monograph 93 (2010)

11. Institute of Medicine, Ovarian Cancers Evolving Paradigms in Research and Care (2016)

12. Armherin, Greenland, & McShane, Retire Statistical Significance 567 Nature 305 (2019)

13. Fedak, et al., Applying the Bradford Hill Criteria in the 21st Century: How Data Integration Has Changed Causal Inference in Molecular Epidemiology, 12 Emerging Themes Epidemiology 14 (2015)

14. Nurses Health Study, Long Questionnaire (1982)

15. Sister Study Personal Care Questionnaire – V3

16. Women's Health Initiative, Form 42 – Observational Study Questionnaire Ver. 1.1

17. Harrington, et al., New Guidelines for Statistical Reporting in the Journal, 381 NEJM 3 (2019)

18. Kenneth Rothman, Six Persistent Research Misconceptions, 29 J. Gen. Intern. Med. 1060 (2014)

19. Supplementary Information to: Retire Statistical Significance

20. Wasserstein & Lazar, The ASA's Statement on p-Values: Context, Process, and Purpose, 70 Am. Statistician 129 (2016)

21. Steffen, et al., Serous Ovarian Cancer Caused by Exposure to Asbestos and Fibrous Talc in Cosmetic Talc Powders – A Case Series, 62 JOEM e65 (2020)

22. Forest Plot: Meta-Analyses and Pooled Studies

23. Forest Plot: Case-Control and Cohort Studies

24. "A Survey of the Long-Term Effects of Talc and Kaolin Pleurodesis." British Journal of Diseases of the Chest 73 (1979): 285–88.

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Appendix C: Deposition Or Trial Testimony Provided In Last Four Years

Depositions (last four years)

U.S. District Court of New Jersey, *In re: Johnson & Johnson Talcum Powder Product Marketing, Sales Practices and Products Liability Litigation*, MDL No. 3:16-md-2738-MAS-RL: March 21, 2024.

Trial Testimony

I have not provided trial testimony.